Toward 100 Anniversary of I.P. Pavlov's Physiological Society

EXPERIMENTAL AND COMPUTATIONAL BIOMEDICINE

Russian Conference with International Participation

in memory of Professor Vladimir S. Markhasin

ABSTRACT BOOK

Ural Branch of Russian Academy of Science

Ural Federal University

named after the first President of Russia B.N.Yeltsin

Ekaterinburg, April 10-12, 2016

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Organizers

Ural Federal University (UrFU)
Institute of Immunology and Physiology (IIP)
Ural Branch of the Russian Academy of Sciences
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Ekaterinburg, April 10-12, 2016

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Сборник содержит тезисы докладов, представленных на российской конференции с международным участием «Экспериментальная и компьютерная биомедицина», посвященной памяти члена-корреспондента РАН В. С. Мархасина (г. Екатеринбург, 10–12 апреля 2016 г.). Основной целью конференции является обсуждение современного состояния экспериментальных и теоретических исследований в области биомедицины.

Сборник предназначен для ученых, преподавателей, студентов и аспирантов биологического и медицинского профиля.

The volume contains the presentations that were made during Russian conference with international participation "Experimental and Computational Biomedicine" dedicated to corresponding member of RAS V.S. Markhasin (Ekaterinburg, April 10–12, 2016). The main purpose of the conference is the discussion of the current state of experimental and theoretical research in biomedicine.

For a wide range of scientists, as well as for lecturers, students of the biological and medical high schools.

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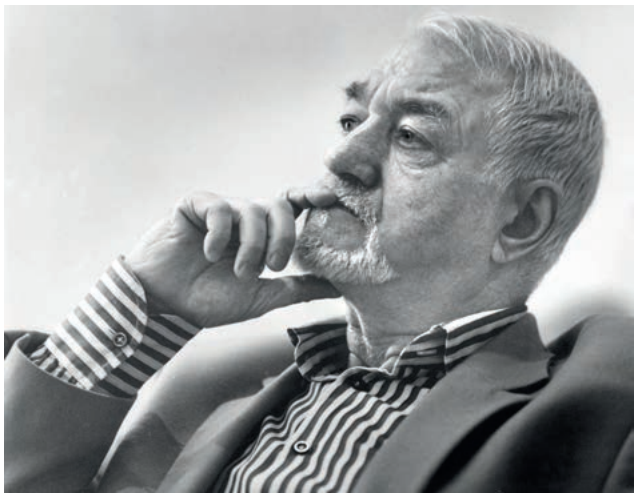

Мархасин Владимир Семенович
(1941-2015)

Markhasin Vladimir Semenovich
(1941-2015)

Год назад, 11 апреля 2015 г., ушел из жизни член-корреспондент Российской академии наук, профессор, доктор биологических наук, заслуженный деятель науки РФ Владимир Семенович Мархасин, выдающийся специалист в области физиологии и биофизики сердечной мышцы. Так случилось, что и другие важные даты его жизни были связаны с апрелем: 23 апреля – день его рождения, в 2016 г. ему исполнилось бы 75 лет, в апреле 2003 г. его избрали в РАН. Владимир Семенович родился в местечке Партала, на границе с Финляндией в семье кадрового офицера. В 1964 г. окончил лечебный факультет Свердловского медицинского института и всегда гордился полученным образованием. Хоть он и выбрал делом своей жизни физиологию, ему было легко сотрудничать с врачами, ставить и решать задачи фундаментальной медицины. Его докторская диссертация посвящена изучению механизмов нарушений ритма у больных врожденными и приобретенными пороками сердца. В 1974 г. Владимир Семенович и Валерий Яковлевич Изаков (он тоже родился в 1941 г., 28 апреля, они вместе учились, работали и дружили) организовали исследовательскую группу, изучавшую физиологию сердечной мышцы. Эта группа потом переросла в лабораторию, а затем стала отделом Института физиологии Коми НЦ УрО РАН. В то время они были одними из немногих в СССР, кто изучал механизмы электрогенеза и сократимости в миокарде, одними из первых начали заниматься математическим моделированием сердечной мышцы. Коллектив приобрел заслуженную известность и авторитет. После смерти В. Я. Изакова в 1990 г. отдел возглавил В. С. Мархасин. Он инициировал новое направление исследований в физиологии сердца – изучение феномена неоднородности миокарда. Под его руководством были разработаны оригинальные экспериментальные и теоретические методы исследования и описан новый класс явлений в биомеханике неоднородного миокарда. Научным коллективом под его руководством выполнены новаторские работы мирового уровня по математическому моделированию в физиологии сердца. В Институте иммунологии и физиологии УрО РАН, организованном на базе его отдела, Владимир Семенович создал лабораторию математической физиологии. Здесь он работал главным научным сотрудником до своих последних дней. В конце 2014 г. стартовал его последний масштабный проект «Персонифицированные компьютерные модели в кардиологии», поддержанный Российским научным фондом. В рамках этого проекта математики и физики вместе с физиологами и кардиологами разрабатывают модели сердца, которые должны помочь ранней диагностике и лечению заболеваний сердца. Профессор Мархасин был настоящим Учителем – ярким преподавателем, заботливым наставником, под его руководством защищено 11 кандидатских и 3 докторских диссертации. Владимир Семенович Мархасин был и останется в нашей памяти истинно преданным науке, глубоким и принципиальным Ученым, честным и порядочным Интеллигентом, неравнодушным, жизнерадостным и остроумным Человеком. Научная школа физиологии, биомеханики и биофизики миокарда, основоположниками которой были Валерий Яковлевич Изаков и Владимир Семенович Мархасин, успешно работает и развивается, молодые исследователи защищают диссертации, студенты начинают свой путь в науке, результаты исследований широко публикуются и признаются международным сообществом.

A year ago, April 11, 2015 a corresponding member of the Russian Academy of Sciences, Professor, Doctor of Biological Sciences, Honored Scientist of the Russian Federation Vladimir Semenovich Markhasin has passed away. He was a leading expert in the field of physiology and biophysics of the heart muscle in Russia. As it happened, some other important dates of his life also took place in April: his birthday was in April 23, in 2016 he would have turned 75 years old, in April 2003 he was elected to the Russian Academy of Sciences.

Vladimir Semenovich was born in the village Partala on the border with Finland in the family of army officer. In 1964 he graduated from Sverdlovsk Medical Institute, acquired excellent education, which he was proud of all his life. Though he chose physiology as the vocation, he was easy to work with doctors, formulate and solve problems of basic medical science. His doctoral thesis was devoted to the mechanisms of arrhythmias in patients with congenital and acquired heart diseases.

In 1974, Vladimir S. Markhasin and Valery Y. Izakov (he was also born in 1941, 28 April, they studied together, were close colleagues and friends) organized a research group to study physiology of the heart muscle. This group developed into a lab, and then became a department of the Institute of Physiology, Komi Science Centre. At that time, they were one of the few groups in the USSR, who studied the mechanisms of electrogenesis and contractility in the myocardium, and among the first started mathematical modeling of the heart muscle. The team has gained a well-deserved reputation and recognition. After the death of VY Izakov in 1990, the department was headed by VS Markhasin. He initiated a new direction of research in the physiology of the heart - the study of the myocardium heterogeneity phenomenon. His team developed original experimental and theoretical research methods and identified a new class of phenomena in the biomechanics of heterogeneous myocardium. They also carried out pioneering works on mathematical modeling in heart physiology. VS Markhasin organized a laboratory of mathematical physiology in Institute of Immunology and Physiology, Ural Branch of Russian Academy of Sciences. Here he worked as a senior researcher until his last days. At the end of 2014 he launched his last project "Personalized computational models in cardiology" supported by the Russian Science Foundation. Under this project, mathematicians and physicists together with physiologists and cardiologists develop models of the heart to contribute to the early diagnosis and treatment of heart disease.

Professor Markhasin was a real teacher - a bright lecturer and caring mentor. Eleven candidate and three doctoral dissertations were defended under his supervision. Vladimir Semenovich Markhasin will always remain in our memory as a perceptive, astute and principle Scientist, innate Intelligent, cheerful, scintillating and witty Man.

Scientific school of physiology, biomechanics and biophysics of the myocardium, which was launched by Valery Y. Izakov and Vladimir S. Markhasin, has been successfully developed: young researchers defend the dissertation, students begin their careers in the science, research results are widely published and recognized by the international community.

Автор фотопортрета С.Г. Новиков
Photo by S.G. Novikov

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Keynote speakers

Amiran Revishvili
Academician of RAS, professor, director of the A.V. Vishnevsky Institute of Surgery, Moscow, Russia

Atrial fibrillation. Noninvasive diagnostic and treatment: from fundamental studies to clinical practice

Irina Roshchevskaya
Corresponding member of RAS, head of Laboratory of Comparative Cardiology, Komi Scientific Center UB RAS, Syktyvkar, Russia

Regularities of the depolarization of an atria: an experimental comparative-physiological study

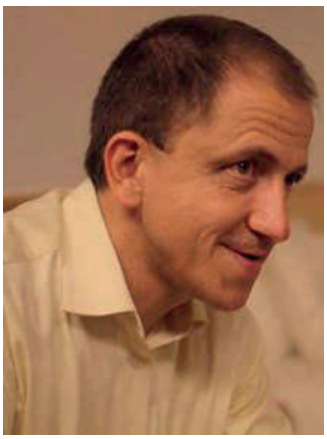
Sergei Fedotov
Professor of Applied Mathematics, School of Mathematics, The University of Manchester, Manchester, UK

Non-Markovian random walks and anomalous transport in biology

Alfons Hoekstra
Associate Professor, University of Amsterdam, Netherlands.
Professor in Computational Biomedicine,
ITMO University, Saint Petersburg, Russia

Multiscale Modelling in Vascular Disease

Keynote speakers



Peter Kohl
Chair in Cardiac Biophysics and Systems Biology, Faculty of Medicine, National Heart & Lung Institute, Imperial College London, London, UK.
Director of the Institute for Experimental Cardiovascular Medicine, University of Freiburg, Freiburg, Germany

Systems Biology of the Heart: Why Bother?

Andreas Meyerhans
ICREA Research Professor, Pompeu Fabra University, Barcelona, Spain.

On the regulation of virus infection fates

Alexander Panfilov
Professor, Departement of Physics and Astronomy, Ghent University, Ghent, Belgium.

Systems approach to studying mechanisms of ventricular fibrillation using anatomically accurate modeling

John Jeremy Rice
Manager, Multiscale Systems Biology and Modeling Group, IBM Research, Yorktown Heights, USA

Life Sciences Research at IBM

Contents

Plenary lectures

Non-Markovian random walks and anomalous transport in biology

Fedotov S.

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What is anomalous transport? It is a widespread natural phenomenon. Examples include movement of proteins on cell membranes, motor-protein mediated active transport inside cells, transport of signalling molecules in the dendrites, bacterial motility, animals and human migration. Anomalous transport cannot be described by standard tools like advection-diffusion equations. Instead it requires the use of linear fractional partial differential equations involving fractional derivatives of non-integer order. The question arises as to how to extend these equations for the nonlinear case involving transport with adhesion, non-linear crowding and biochemical reactions. The talk is concerned with new nonlinear and non-Markovian random walk models developed in the recent years. We present the nonlinear fractional equations and show how to apply these equations to the anomalous chemotaxis, morphogen gradient formation and intracellular superdiffusion.

Multiscale modelling in vascular disease

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I will introduce our ongoing work on the Virtual Artery, a multiscale model for Vascular Disease. Both the arterial wall and blood are modelled on the cell level and tissue level, and are all coupled together into a tightly coupled multiscale model, which in turn is coupled to whole body models for blood flow. I will show examples of applying the Virtual Artery in modelling thrombosis in intracranial aneurisms and in modelling in-stent restenosis in stented coronary arteries.

Systems biology of the heart: why bother?

Kohl P.

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Systems Biology has moved from a theoretical idea, or rather a disparate set of ideas, to a mainstream feature of research activities and funding priorities. Institutes, departments and centres of various flavours of Systems Biology have sprung up all over the world. An internet search will now produce more than 60 million hits (compared to <6 million in 2010). Out of PubMed's 8,700 entries with "Systems Biology" in either title or abstract, only 2 (two) papers are pre-2000, while more than two thirds were published since 2010. Still, there seem to be more questions than answers when one discusses the topc: What is systems biology? How does it differ from classic biomedical research? Do we need it? What is the role of computer models in this context? Can they be relied on? Can computer simulations replace experiments on biological samples, including living animals? When will we have an all-inclusive model of a real patient? This lecture will attempt to address the above questions, using illustrations from heart research. Aims: provide conceptual background, introduce definitions, provide examples of the systems research approach to integration and reduction of data

related to cardiac structure and function – with the aim of turning data into information. Objective: highlight the need for multi-level (ion channel to ECG) and multi-type (e.g. experimental and theoretical) model systems, for quantitative projection between basic science and clinical relevance. Take home message: it is hoped that at the end of the lecture, we will be able to explain 'systems biology' as an approach, define the term 'model', and illustrate the concepts associated with these terms on one or two examples. Further reading: Combining wet and dry research: http://www.ncbi.nlm.nih.gov/pubmed/23334215 Systems biology: an approach: http://www.ncbi.nlm.nih.gov/pubmed/20531468

On the regulation of virus infection fates

Meyerhans A.

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Viral infections can be fundamentally categorized as acute or persistent according to their temporal relationships with their hosts. In an acute infection, virus-specific T-cells become activated, proliferate, and differentiate into effector T-cells, allowing the virus elimination within a few weeks. By contrast, persistent infections, such as the caused by HIV and HCV, are not resolved and develop when T-cells become exhausted, i.e. differentiate into a state with poor effector function to avoid immunopathology. In my presentation I will describe ongoing work of my group that aims (i) to understand the mechanisms of how exhaustion is established and (ii) to identify strategies of immune interventions for shifting the dynamic equilibrium between virus expansion and immune control.

Systems approach to studying mechanisms of ventricular fibrillation using anatomically accurate modeling

Panfilov A.V., Dierckx H., Kazbanov I., Vandersickel N.

Ghent University

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We report on the development of anatomically accurate model of ventricles of the human heart. The model integrates our knowledge from a single cell to the whole organ and allows us to study mechanisms of cardiac arrhythmias in the human heart, where experimental interventions are very limited. We will present and discuss our recent research using this model. It includes studies of ventricular fibrillation during global ischaemia and quantification of the relative contributions of the hypoxia, acidosis and hyperkalemia on the changes in the fibrillation frequency and complexity. We have also studied arrhythmias which occur as a result of early after depolarizations (EADs). EADs occur in many forms of genetic defects such as the long QT syndrome or under the action of pharmacological agents as a result of cardiotoxicity. We also present our studies on the arrhythmias which occur due to fibrosis of cardiac tissue. We discuss importance of heterogeneity for the onset of the arrhythmias and recently found effect of attraction of sources of arrhythmia to the regions with a high degree of fibrosis. Finally we discuss possibilities of application of our approaches to clinic.

Atrial fibrillation. Noninvasive diagnostic and treatment: from fundamental studies to clinical practice

Revishvili A.S.

A.V. Vishnevsky Institute of Surgery

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This study aimed to identify sources of initiation and maintenance of atrial fibrillation (AF) by means of surface ECG based mapping technology combined with CT scan or MRI. Methods. We applied noninvasive mapping using 240-lead ECG (Amycard LCC) to 23 patients (15 male/8 female) with paroxysmal and persistent AF. Results. During evaluation of electrical activity in the left and right atrium we found from 2 to 4 simultaneously coexisting «rotors». Targeted ablation terminated AF and maintained sinus rhythm in 8 patients (35%). In 15 patients (65%) we registered prolongation of arrhythmia cycle length but its termination was achieved only after pharmacological or electrical cardioversion. Conclusion. Initial experience with noninvasive ECG imaging using 3D-4D mapping system combined with CT scan or MRI shows its clinical utility, feasibility to provide noninvasive evaluation and features of arrhythmogenic areas and to increase effectiveness of interventional AF treatment.

Life sciences research at IBM

Rice J.

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Cardiac models are increasingly being developed toward a goal of treating patients in the clinical setting. Additionally, cardiac models continue to grow in sophistication and predictive value. A key question for the field is how to best incorporate patient-based data to allow for accurate representations of patient physiology and pathophysiology. This talk will cover work in our group to increase the predictive power of cardiac models and also how to incorporate personalized data including genomic, anatomical and functional data. We show an example in which the risk of arrhythmia in Long QT 1 patients could be predicted based on a combination in vitro data to characterize the genotype to phenotype relation and an in silico model to predict physiological responses.

Regularities of the depolarization of an atria: an experimental comparative-physiological study

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Regularities of the depolarization of atrial myocardium are discovered by the experimental comparative-physiological studies of excitation waves propagation in atria for different animal species with different types of the heart ventricles activation. In experimental models of hypertension the increase of the heterogeneity of the atrial depolarization is shown, leading to the risk of arrhythmias. The heterogeneity of animals' atrial depolarization with a different architectonic of the conductive system and the myocardium fibers is an experimental basis for the computer simulations.

Scientific basis for development of antiviral drugs

Rusinov V.L.[1], Chupahin O.N.[1,2], Charushin V.N.[1,2]
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A new class of nonnucleoside antiviral substances was revealed. Antiviral drugs may be produced using the obtained data. The first drug based on this class of compounds called trisaverin was approved for consumer sale in 2009-2013. Trisaverin is effective for treatment of influenza virus infection, RS virus, parainfluenza, adenovirus, tick-borne encephalitis and hemorrhagic fever. Hemagglutinin, which is the protein of virus, is the target for trisaverin. The modeling of interaction between trisaverin and hemagglutinin showed noncovalent interaction between this drug and the protein. Trisaverin demonstrates oxidative activity. The formation of tertiary structure of hemmaglutinin and life cycle of virus are failed.

Tribute Lecture. Mechano-electric heterogeneity of the myocardium as a paradigm of its function

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[3]Institute of Mathematics and Mechanics UB RAS
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Myocardial heterogeneity is well appreciated and widely documented, from sub-cellular to organ levels. This talk reviews achievements of the group, led by Professor Vladimir S. Markhasin, Russia, who was one of the pioneers in studying and interpreting the relevance of cardiac functional heterogeneity.

Myocardial energy starvation in chronic heart failure: perspectives for metabolic therapy

Veksler V.
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Energy metabolism and mitochondrial biogenesis disorders appear to play an important role in cardiac dysfunction and progression to heart failure (HF). Studies showing that chronic HF is associated with depressed energy production and altered intracellular energy transfer, have led to the concept of energy starvation. Our works have revealed that mitochondrial function in cardiac and skeletal muscle in HF exhibits defective oxygen consumption and mitochondrial regulation that correlate with decreased mitochondrial protein content leading to limited ATP synthesis capacity and high-energy phosphate kinetic abnormalities. This is linked to the disturbed gene expression of mitochondrial proteins controlled by the peroxisome proliferator-activated receptor gamma co-activator-1alpha (PGC-1α) and its downstream transcription cascades, which are down-regulated in HF. Activation of post-translational pathways controlling PGC-1α activity could be a promising approach in metabolic therapy of HF.

Fetal cardiac assessment using new methods of ultrasound examination

Wladimiroff J.W.
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A four-dimensional (4D) fetal echocardiographic technique utilizing spatiotemporal image correlation, tomographic ultrasound imaging display (STIC-TUI echo) and color Doppler has previously been shown to be effective in displaying the examination planes constituting the extended cardiac examination. The aim of this study was to evaluate the performance of this first-trimester STIC-TUI echo technique in identifying complex congenital heart disease (CHD) in high-risk pregnancies. First-trimester 4D echocardiography using a standardized application of STIC, TUI and color Doppler imaging is effective in displaying the imaging planes that are necessary for achieving the diagnosis of complex cardiac anomalies in high-risk patients. Optimal imaging of the four-chamber view with two-dimensional ultrasound is the major determinant of successful volume acquisition.

The important questions of regeneration theory

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The restoration of functional elements of damaged organs such as connective tissue, microvasculature, nerve fibers is very important. Different types of cells such as fibroblasts, macrophages, lymphocytes, stem cells, mast cells, endothelial cells, platelets involve in the regenerative process. A lot of mediators such as HGF, SDF-1, glycosaminoglycans, NNF-alfa, interferon-gamma, VEGF, PDGF, TGF-b, PDEGF, IGF-1, FGF, EGF etc. provide the interaction between the cells during regenerative process. An increase in regeneration is accompanied by activation of apoptosis in cells.

Experimental and computational models in cardiovascular physiology and cardiology

T-wave area along with Tpeak-Tend interval is the most accurate index of the dispersion of repolarization

Arteyeva N.

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BACKGROUND. It has been proven that Tpeak-Tend interval is an accurate index of ventricular dispersion of repolarization (DOR), but its clinical use is rather complicated because it's difficult to determine the T-wave end. In this regard, there is a need in the alternate methods of DOR evaluation. METHODS. In the present simulation study we used the discrete computer model of the rabbit heart ventricles. The magnitude of DOR and action potential durations (APD) in the model were varied in a wide physiological range. The magnitude of DOR was compared to the simulated T-wave amplitude, T-wave area and Tpeak-Tend interval. RESULTS. The relationship between the T-wave amplitude and DOR was nonlinear, lead-dependent and largely affected by APD. On the contrary, both Tpeak-Tend interval and T-wave area showed a good correlation with DOR regardless of APD range. The study was supported by the comprehensive program for basic research of UB RAS (project № 15-3-4-16).

Mathematical modeling of the calmodulin effect on the RyR2 gating

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Ryanodine receptors (RyRs) play key role in the excitation-contraction coupling (ECC), they mediate the release of calcium ions from the sarcoplasmic reticulum. Calmodulin CaM is a ubiquitous cytosolic Ca^{2+} binding protein that modulates cellular events such as ECC through the CaM-dependent protein kinases or by a direct binding to ion channels, such as RyR, giving rise to its inhibition. Here we address a simple physically clear electron-conformational model to describe the RyR gating and argue that the main effect of the CaM binding can be reduced to a change of the energy separation between the RyR's open and closed electronic states. Results of the computer modeling allowed us to reproduce successfully the CaM inhibition of RyR2: decrease in Popen and , increase in and less effective inhibition at higher [Ca^{2+}].

Contribution of cooperativity to the mechano-calcium feedbacks in myocardium. Experimental discrepancy and mathematical approach to overcome it

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Mechano-Calcium Feedbacks (MCFs) provide a fine tuning of electrical and calcium activation to mechanical conditions of myocardium contractions. Experimental and theoretical works testify to the cooperative dependence of CaTnC kinetics on the cross-bridge concentration as a key mechanism underlying MCFs in the intact myocardium. However experiments on skinned heart muscles show that the muscle length negligibly affects Hill's coefficient of cooperativity of the 'pCa-force' relation. We suggest a refined concept of the cooperativity providing for both mechano-dependence of calcium activation in the intact heart muscles and alleged "insensitivity" of the 'pCa-force' mechano-dependence to the cooperativity in skinned ones. The concept incorporated in a mathematical model makes cooperativity reveal itself differently in steady-state (for skinned muscle) and transitional processes (including intact myocardium twitches). Supported by the Ural Branch of the RAS Program (project 15-5-4-8).

The stochastic and chaotic estimation of parameters of cardiorespiratory system of students of Ugra

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Human ecology covers a very important issue of life expectancy between the indigenous and alien population of the Northern territories of the RF. In this regard, we performed a comparative analysis of parameters of HRV pupils, which indigenous and non-indigenous people of Ugra. The analysis was performed by the method of multiple comparisons of the three age groups of schoolchildren and the method of calculating inter-cluster distances. The differences in the dynamics of age-related changes in the schoolchildren of Ugra and the distinctive trends of the parameters of heart rate variability between indigenous and non-indigenous representatives of the North. In particular, revealed a higher adaptive capacity of aboriginal representatives in comparison with the migrant population. Age-related changes in SSS girls representing the indigenous population of Ugra, have a more pronounced dynamics on a number of parameters in comparison with non-indigenous residents, who are by characterized.

Characteristics of the accuracy of calculation of values of systemic Blood pressure using transfer functions in experimental blood loss

and its compensation

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Objective: comparison of the errors of application of transfer function (TF) for the evaluation of systemic arterial pressure (AP) after blood loss and its compensations. In the experiments on rats, AP was synchronously registered in the carotid and femoral arteries in a state before blood loss after modelling acute hemorrhage and dextran infusion. Having computed TF, values of AP in the carotid artery and systemic errors (SE) were calculated. The vascular rigidity was estimated using measurements of pulse wave velocity (PWV). The values of AP, PWV and SE after blood loss and its compensations were compared using paired Wilcoxon test. It is shown that, hemorrhage causing the reduction of vascular rigidity, increased SE. Compensation of the circulating blood volume by means of dextran infusion resulted in restoration of both vascular rigidity and SE of estimated AP. The results can be put into medical practice as an approach for testing non-invasive methods in cardiovascular research.

Mechanisms of cardiodepression after 80% liver resection in rats

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Direct assessment of contractile function and myocardial metabolism of isolated hearts was performed in control and after 1, 3, 6, 12 hours and 1, 3, 7 days after 80% liver resection in rats. Pressure in the left ventricle was recorded, the content of glucose, lactate, aspartate aminotransferase activity in the coronary perfusate were determined in these periods. It was revealed that acute systolic-diastolic left myocardial dysfunction developed in the first hours after surgery. Hearts of operated animals were less resistant to hypoxic damage and reoxygenation, consumed more glucose per unit of function, and excreted more lactate and aspartate aminotransferase in coronary flow compared to control. Thus, inhibition of the contractile myocardial function because of hypoxia, inhibition of energy metabolism, mitochondrial dysfunction and damage of the membranes of cardiomyocytes occured in the early period after surgery.

Aging dynamics of cardio-vascular parameters aboriginal system and alien population of the Russian North

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It was presented the aging evolution of biological systems as the example of changing the cardio-vascular parameters and values of the quasi-attractors and Shannon entropy of women and man body of three age groups of indigenous and alien population of Ugra. Parameters xi of the cardio-vascular system of the three age groups of women and man ranged limiting volume VG of the phase space of states, which are defined as quasi-attractor. According to the Native Women's aborigines quasi-attractor parameters the population of Ugra build models Ferhlyust-Pearl. A woman and man who is not aborigines changes it

parameters of quasi-attractors as a parabolic relationship with a minimum average age. Now we present a real evolution of biosystems (transition from one stable state to another). It was presented common criteria for estimation of pathological or normal state of human body. Numerical examples of such evolution was presented too.

Photocontrol of voltage-gated ion channel activity by azobenzene trimethylammonium bromide in neonatal rat cardiomyocytes

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As the activity of voltage-gated ion channels mainly controls the membrane potential of cardiac cells, this study examined whether the sensitization effect of azoTAB was exerted primarily via the modulation of ion channel activity. The effects of trans- and cis-isomers of azoTAB on voltage-dependent sodium (I_{Nav}), calcium (I_{Cav}), and potassium (I_{Kv}) currents in isolated neonatal rat cardiomyocytes were investigated using the whole-cell patch-clamp technique. The results show that azoTAB modulates ion currents, resulting in suppression of sodium (Na^+) and calcium (Ca^{2+}) currents and potentiation of net potassium (K^+) currents. This finding confirms that azoTAB-effect on cardiac tissue excitability do indeed result from modulation of voltage-gated ion channels responsible for action potential.

The application of C-TAB for excitation propagation photocontrol in cardiac tissue

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Cardiac cell tissue is widely used to for studying mechanisms of cardiac arrhythmias and for developing approaches to cure such lethal diseases. The assays using excitable media need various methods of setting their properties for modeling pathological regimes of excitation generation and conduction. Photocontrol is one of the ways to affect excitation propagation (to create obstacles or artificial inhomogeneity) without a serious invasion and cell damage. The basis of this method is applying special photosensitive molecules. In our work the photosensitive molecule C-TAB was examined for its cytotoxicity and blocking effect on the excitation propagation. The blocking effect of the active UV-irradiated form of C-TAB was demonstrated on neonatal rat cardiomyocyte monolayer. At the lower concentrations of C-TAB it was shown that propagation speed decreases with the increase of the substance concentration and elongation of UV-exposure. The toxic effect of C-TAB was examined on 3T3 fibroblast with MTT method. C-TAB appeared to be 10 times less cytotoxic than the latest analogue Azo-TAB.

Localization of TRPC3 channels estimated by in-silico and cellular functional experiments

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Transient receptor potential canonical (TRPC) channels are known as stretch-activated non-selective cation channels that mediate stretch-induced changes in Ca^{2+} handling/signaling in cardiac muscle. Although their intracellular localization is important in the context of their role in the cellular Ca^{2+} handling, findings about their localization in immunochemical studies are inconclusive between sarcolemma and sarcoplasmic reticulum (SR) membrane. To predict it, we investigated the role of TRPC3 channels on stretch-induced changes in Ca^{2+} transient and SR Ca^{2+} content in isolated mouse cardiac myocytes using carbon fiber technique in combination with mathematical modeling study. We found that wet-experimentally obtained response to stretch was reproduced only by the model with sarcolemmal stretch-activated cation channels, suggesting TRPC3 channels are at least located on sarcolemma.

Conditions of the spiral wave unpinning from the heterogeneity with different boundary conditions in a model of cardiac tissue

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This research aims to reveal the main patterns of various defects in cardiotissue. To investigate nature of inhomogeneities we design experimental scheme. In addition, we model such inhomogeneties in silico. Finally, we compare experimental data with quantitative results to build computer model of defects. All of this allows us to outline the main features of unpinning and to predict some effects.

The influence of anisotropy on excitation wave propagation in neonatal rat cardiomyocytes monolayer

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This work is devoted to various models of the cardiac arrhythmias and the modeling of the spiral wave formation, in particular. To create controlled anisotropy in the cultured cell layer for cardiac arrhythmias models we used a photosensitive agent AzoTAB. In this paper, two main models have been created: the model of unidirectional block and the model with a gradient of excitability. The model of an unidirectional block relies on a creation of inhomogeneous excitability in the tissue, which describes the main mechanism for the formation of a circulating wave. UV-light lowers the activation threshold of excitation, so in a presence of abrupt UV gradient excitation wave propagates only from the non-irradiated area to the irradiated one. A modeling of spiral waves drift in a gradient of excitability in the monolayer of cardiomyocytes is based on the critical degrees of excitation determined in the first model. Spiral wave, formed in such gradient of excitability, drifts more frequently towards lower excitability.

The designing of vectorcardiograph prototype

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The apparatus for vector electrocardiogram (VCG) recording has developed. The work principle has been considered and technical characteristics of developed apparatus based on Frank's formulas are justified. The VCG recording procedure has been described. The way of electrocardiogram (ECG) from vector electrocardiogram synthesis has been analyzed. Confidence limits of VCG diacrisis parameters have been obtained.

Models of chronic heart failure with acute and gradual onset

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Chronic heart failure (CHF) can have a different etiology. We studied myocardial changes at acute HF induced by isoproterenol and gradually developed CHF induced by doxorubicin. Application of isoproterenol to rats in cumulative doses of 240-360 mg/kg (2 injections in 2 days) was accompanied by early 15-40% mortality. The surviving animals which received smaller doses, exhibited diastolic CHF with normal contractility but decreased relaxability, and received larger doses - the systolic CHF with decreased contractility and pronounced dilatation of the heart. In isolated cardiomyocytes, various violations of calcium signals were found. Application of doxorubicin (weekly injections of 2 mg/kg within 6-8 weeks) resulted in term-dependent mortality, progressive decrease in ejection fraction and other indicators of left ventricular contraction as revealed by echocardiography. Similar data were obtained at catheterization of the left ventricle, moreover, relaxation indices always fell more profoundly than contractility indices at any term. In conclusion, the extent of myocardial damage determines the development of diastolic or systolic CHF.

Remote Patient Monitoring and Integration of Medical Data

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Rapidly growing application of Home Monitoring (HM) pacemakers and implantable cardioverter-defibrillators for remote patient monitoring led to a new medical service. It establishes a closed information loop "patient – service centre – physician – patient" for early diagnostics and personalized therapy of patients with heart diseases. Implants with supplementary smartphone based transmitters provide to the HM service centre an extensive data on patient's physiological parameters and intracardiac electrograms of clinically relevant episodes. In 2014, Russian Scientific Society of Arrhythmologists started the ReHoming project (Registry Home Monitoring) not only localizing the HM technology in Russia and Kazakhstan but also introducing the screening centre strategy into wide clinical praxis. Thus, the study internet portal rehoming.dicoming.com enables anonymized medical data integration for automatically upgrading statistical analysis and mathematical processing. Becoming an instrument for clinical outcome improvement the HM technology opens new opportunities for

epidemiological research and preventive healthcare.

Markov chain for an indicator passing throughout cardio-vascular system (CVS).

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Cardio-output (CO), heart volume (HV) and some other parameters are obtained from an indicator dilution curve. There are many algorithms to treat a curve and some problems with checking their quality. Our aim is to develop a math model of CVS trhat can be used to check algorithms. Such model can be developed if we accept that within CVS there are segments with different flow. They are (1) Heart. Equations for heart are based on the statement: heart chambers are pumps with geometric distribution for time to pass. (2) Conductive vessels. They connect microcirculation and heart and time to pass is named a delay. (3) Microcirculation. It has two properties (a) there is dispersion in length of microvessels, (b) the flow in each microvessel is irregular. Thus a compound Poisson distribution describes a microcirculation. Model of CVS is the composition of named systems. Experiments on PC reveal that by changing parameters of the model one can produce all types of dilution curves including those with intracardial shunts or one-ventricle heart.

Influence of myocardial heterogeneity on scroll wave dynamics in an axisymmetrical anatomical model of the left ventricle of the human heart

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Myocardial tissue is known to be heterogeneous and highly anisotropic. We studied the influence of apico-basal and transmural heterogeneity on the dynamics of scroll waves in isotropic and anisotropic cardiac tissue using our axisymmetrical anatomical model of the left ventricle [1] and Aliev-Panfilov electrophysiological model of cardiac excitation. We showed that small apico-basal heterogeneity has minimal effect on the position of the scroll wave filament, however it substantially affects filament drift speed by increasing it in 5-60 times. If the heterogeneity is more than 45%, it dominates filament dynamics and filament shifts to the region of longer action potential duration. Transmural heterogeneity is essential only for the anisotropic heart model and results in shift of the vortex to the ventricular base.
1. S. F. Pravdin, V. I. Berdyshev, A. V. Panfilov, L. B. Katsnelson, O. Solovyova, V.S. Markhasin, Biomedical Engin. Online. 54, 12 (2013). Supported by RSF grant 14-35-00005.

An improved analytical model of the cardiac left ventricle

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We develop an improved mathematical model of the shape and myofibre orientation field in the left ventricle (LV) of the human heart based on our analytical LV model (Pravdin et al., 2013). Here we consider the LV as a rotation body consisting of two parts - a basal and a lower equatorial-to-apex part. Each part is composed of a set of myocardial surfaces (sheets) which are formed of a continuum of curves simulating myocardial fibres. Tangents to these curves create a myofibre direction field. To simulate the LV shape, we define parameters such as the equatorial LV radius, height of the parts, wall thickness at several longitudinal levels and some others. Using explicit analytical formulae, we construct muscular layers as spiral surfaces and myofibres as curves on them. For the model personification, we fit meridional LV sections from MRI or CT images of the LV. Then we interpolate parameters between meridional sections and construct the whole LV body.
Supported by RSF grant 14-35-00005.

Sex-related effects of stretch on isometric twitch and Ca^{2+} transient in healthy and failing right ventricular myocardium of adult and impuberal rats

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We compared the sex-related effects of stretch on isometric tension/Ca^{2+} transient in right ventricular trabeculae of adult and impuberal healthy rats and rats subjected to monocrotaline (MCT) to develop RV failure. In adult rats (6-mo old), MCT resulted in RV hypertrophy, blunted force-length relation, substantially prolonged twitch/Ca^{2+} transient in males only (vs. same-sex healthy rats). In impuberal rats (~1.7mo old) treated by MCT, both males and females suffered from RV hypertrophy and showed deficient force-length relation as well as substantially prolonged and attenuated twitch/Ca2+ transient (vs. same-sex healthy rats). In conclusion, the pathological remodeling of rat RV myocardium in chronic pulmonary hypertension (triggered by monocrotaline) depends on the stage of pubescence. Sex hormones of adult female rats impede the remodeling which does blunt the Frank-Starling mechanism in adult male rats. Impuberal rats are deficient with this protective effect of sex hormones.

Electron-conformational model of the ligand-activated ion channels

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Electron-conformational (EC) transformations are of a principal importance for the gating of the ligand-activated ion channels, in particular, Ca^{2+} activated ryanodine receptors (RyRs) that play a key role in the excitation-contraction coupling mediating the release of calcium ions from the sarcoplasmic reticulum. In the talk we consider fundamentals of the electron-conformational theory focusing on the modeling the RyR2 channel in cardiomyocites and

pacemaker cells. We show that a simple biophysically based electron-conformational model of the RyR2 channel is able to explain and describe on equal footing all the features of the isolated RyR2 gating and the concert of the coupled RyRs in the release units for ventricular myocytes and sinoatrial node (pacemaker) cells. Despite the EC model is intentionally simplistic, it offers novel insight into potential mechanisms governing by the Ca^{2+} fluxes and may thus provide a starting point for further exploration of physical principles guiding cardiac cell functioning in vitro and in vivo. Supported by the Russian Science Foundation, project #14-35-00005.

In silico comparison of the electrical propagation wave along myocardium fibers in the left ventricle wall vs. isolation

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Correlation between the propagation speed of the excitation wave in the fibers in myocardium and isolated fibers is an important question for understanding the electrophysiological processes of the heart. We based our work on the left ventricle anatomical model [1] and Aliev-Panfilov electrophysiological model of cardiac excitation. We found that even if diffusion coefficients along fibers in 3D and 1D models are equal, the propagation speed of the excitation wave in majority of myocardial fibers is significantly higher than in same isolated ones. This can be explained by the fact of electrical quasi-isotropy of the 3D myocardial medium caused by the fiber rotation within the wall. Supported by the Russian Science Foundation №14-35-00005.

1. S.F. Pravdin. Nonaxisymmetrical mathematical model of the cardiac left ventricle anatomy. Russian Journal of Biomechanics, 17, № 4 (62):84–105, 2013.

Valid method for estimation of pulmonary hypertention degree in children

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The term "pulmonary hypertension" (PH) brings together disorders characterized by a progressive increase in pulmonary vascular resistance, which leads to the right heart failure and premature death. The average lifespan of children from the moment of diagnosis is 2-3 years (Okumura K et al., 2014). A high correlation was found between degree of PH, serotonin and hydroxyindoleacetic acid (5-HIAA) concentrations in the blood. By immunoassay concentrations of 5-HIAA in the urine of children with various degrees of PH was measured and the correlation between these two parameters was revealed. The serum serotonin was measured in children with varying degrees of PH. An analysis of 5-HIAA in the urine was performed twice (before and after surgery). There was a significant (in 1,5-7,2 times) decrease in the concentrations of 5-HIAA in the postoperative period, which suggests the possibility of using the method as valid for estimation of the effectiveness of treatment with PH.

Mathematical modeling of the cardiovascular system under the influence of environmental factors

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The mathematical cardiovascular system work model is developing. Work is carried out in an integrated modeling of major organs and systems functioning. The most important characteristic of the model is the consideration of functional disorders caused by the adverse effect of environmental factors, aging and lifestyle. The main task of the modeling is forecast of functional disorders of the cardiovascular system after a specified time interval. It is necessary for the timely adoption of measures for individual.

Adaptivity of the alternating direction method for fractional reaction diffusion equation with delay effects in electrocardiology

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Zeng et al. introduced the effect of time delay in the FitzHugh–Nagumo neural model with correlations between multiplicative and additive noises. An investigation of the spatio-temporal effects of a space-fractional models in electro-cardiology were provided due to the use of space fractional operators in reaction-diffusion models to describe how electrical currents flow through the heart controlling its contraction. Liu et al. developed a new fractional FitzHugh-Nagumo model. We first consider the two dimensional space fractional reaction-diffusion equation with delay effects in the time component on an irregular domain as a general case for all reaction-diffusion models in electro-cardiology. The alternating direction scheme with detailed analysis for the order of the approximation error, unconditional stability and convergence order is constructed for the numerical solution of these equations.

Influence of alcohols on excitation wave propagation in neonatal rat ventricular cardiomyocyte monolayer

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Alcohols take a particular role in QT-prolongation and inhibition of voltage-dependent ion channels. Heptanol is used in electrophysiology as a gap-junction blocker. In this work we investigated the velocity of excitation wave propagation and critical capturing frequency in neonatal rat ventricular myocyte monolayer as a function of ethanol and heptanol concentration. With the both alcohols at concentrations from 0.1 mM to 2.2 mM excitation propagation velocity has decreased exponentially. In the experiments with heptanol, at concentrations between 1 and 1.8 mM velocity decreased from 27 mm/s to 14 mm/s. Conduction block took place at 1.8 mM, which indicates the uncoupling role of heptanol for the cells. Unlike the ethanol, at concentrations 0.8-1.4 mM velocity dropped by 80% so the length of propagating impulse decreased considerably. Consequently, the size required for the existence of reentry was considerably smaller. This fact may represent pro-arrhythmogenic action of the ethanol.

A mathematical model of the cardiac left ventricle

anatomy and morphology

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We describe a mathematical model of the shape and fibre direction field of the cardiac left ventricle (LV). The ventricle is composed of surfaces (they model myocardial sheets) filled by with curves corresponding to myocardial fibres. The input data for the model is only the LV shape. A number of models of concrete normal canine and human LVs were constructed based on experimental DT-MRI data. Based on this model, one can construct a numerical mesh for simulating LV electrophysiological and mechanical activity. A special coordinate system is set in the model so that the LV is a bar there. This simplifies writing the boundary conditions. By changing the model parameters, one can set a general or regional ventricular wall thickening or the LV shape change, which is typical for certain cardiac pathologies. The model has been used in many simulations studying electrical processes in norm and pathology. Supported by RSF grant 14-35-00005.

Cause and effects of cardiac heterogeneity: insights from experimental and computational models

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One obvious effect of ventricular electrophysiological heterogeneity is the concordant nature of the R and T waves in the ECG. But what is the evolutionary cause of this heterogeneity? Most probably, the driving force is mechanical function as contraction uses roughly 90% of the consumed energy. Furthermore, synchronicity in mechanical action is favored as it is a state in which cellular force is most optimally translated into ejection of blood. As electrical activation happens as a sequence lasting around 100ms, this delay has to be homogenized for the mechanical process. Therefore, cells from early activated sites should take a longer time to reach their respective maximal force than late activated sites. The heart can achieve this by different density, and function of proteins which form ionic channels and mechanical units of individual cells. On the macroscopic scale - this is heterogeneity. This talk is showing evidences supporting this theory from experimental and computational models.

Basic metabolomic patterns in early hypertensive rats: MRI study

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Magnetic resonance imaging (MRI) is well established as a suitable non-invasive method to examine various functional structures in vivo. The technique of localized one-voxel magnetic resonance spectroscopy (MRS) was applied to estimate the brain metabolites ratio in cerebral cortex and hypothalamus of hypertensive ISIAH and normotensive WAG rats (1.5 mo-old). The research was carried out in SPF-vivarium of IC&G SB RAS (RFMEFI61914X0005, RFMEFI61914X00010). The increased arterial pressure in ISIAH rats is positively correlated with prevalence of the excitatory metabolites (glutamate+glutamine) and markers of neuronal energetic activity (creatine+phosphocreatine, taurine) in cerebral cortex. On the contrary, the ratio of excitatory to inhibitory neurotransmitters in hypothalamus of ISIAH rats showed prevalence of the inhibitory ones (GABA). The concentrations of creatine and N-

acetylaspartate were also reduced in hypothalamus of ISIAH rats. The study was supported by grant 14-15-00118 from the Russian Science Foundation.

Modeling of cardiac arrhythmia generation caused by pathological distribution of myocardial conductivity

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The effect of spatial inhomogeneity on cardiac arrhythmia generation is investigated in terms of the Aliev-Panfilov phenomenological model. One of the parameters of inhomogeneity is the conductivity of cardiac muscle varying from the normal value to zero, which is typical of the infarct scar. An arrhythmia can be caused by waves propagating around non-conducting tissues. The process of cardiac arrhythmia can be triggered on a tissue segment with unidirectional conductivity. Such conductivity is reached in a narrow channel between the two infarct scars on condition that the channel gradually widens towards one side. Taking as a basis this mechanism and extended it to the regions of low conductivity, we have constructed a 15 mm low-conductivity inhomogeneity, which leads to self-excitation. The inhomogeneity of such size can be readily implemented in the model of human heart on approaching two scars. This work was supported by RFBR (project № 14-01-96032-r_ural_a)

Contractile micro-constructs from cardiac tissue culture for the research of autowave propagation in excitable systems

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A huge variety of model systems for biophysical research could be created with the use of modern tissue engineering methods. During last few years the rapid development of so-called soft-lithography techniques significantly expanded our opportunities for the creation of bio-contractile micro-systems. In present work several types of bio-contractile micro-constructs were developed. Polymer scaffolds for these micro-constructs were made of thin polydimethylsiloxane films of various configurations. Neonatal rat cardiomyocytes were cultured on the surface of these scaffolds. The obtained bio-contractile constructs were used as experimental models for the investigation of excitation-contraction wave propagation in cardiac tissue culture. Some of the developed bio-contractile micro-constructs seem to be of a particular interest for the development of lab-on-chip test systems.

Computational study of the haemodynamic significance of the stenosis during multivessel coronary disease

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Multivessel coronary atherosclerosis is widespread disease. It frequently results in disability or death. Regular angio-surgical treatment consists in endovascular procedure (stent placement). Several stents should be installed in the case of multivessel disease, which may be expensive and not optimal. The expert decision should be based on analysis of haemodynamic significance of every stenosis. Fractional flow reserve (FFR) is all over the world golden standard to solve this problem. We provide an algorithm of FFR assessment by computational model of haemodynamics based on 1D network dynamical model of the flow of viscous fluid through the network of elastic tubes. Data from real patients are used as inputs for the model. Simulated values of FFR are compared to the data from real patients. Variations of FFR due to different factors including vessel's stiffness, cardiac output, autoregulation response rate are evaluated.

A numerical simulation of changes in the performance of the left ventricle of the heart under various hemodynamic conditions

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An axisymmetric model of the left ventricle of the heart is suggested. The left ventricle is approximated by a thick-walled cylinder that consists of myocardial tissue. Myocardium is assumed to be incompressible anisotropic elastic material with finite deformations and stresses specified by the following components: hyperelastic isotropic stress, anisotropic stress of the elastic protein titin, and anisotropic active stress defined by a kinetic model of contraction of cardiac muscle and its regulation, which was developed earlier. The axes of anisotropy are directed along the muscle fibers, which are aligned along helices with the helical angle changing linearly through the wall of the cylinder. It is shown that the model reproduces some dependencies of the ventricle performance (stroke volume) on its pre- and afterload as well as the changes of hemodynamic parameters of the heart cycle upon the conditions of aortic valve stenosis and insufficiency.

A simple model of cardiac muscle: mechanics, actin-myosin interaction and Ca-activation

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A model of mechanics and regulation of cardiac muscle contraction was designed for its further use in multi-scale heart models with a special attention to the computational cost and limitation of the number of the model parameters. The model uses an 'ensemble average' approximation for the description of actin-myosin interaction, simple kinetics of calcium regulation and a continuum mechanics approach for the formulation of constitutive

equation for the stress tensor. The model describes well a number of experiments with fully activated skeletal muscles and twitch contractions of cardiac muscle including steady-state contractions, responses to step changes in length or load, force responses to length oscillations as well as length-dependent activation and load-dependent relaxation. The model can be combined with a simple model of action potential for simulation of the electromechanical coupling in cardiac muscle in situ and in vivo.

Calcium-current dominated upstroke in severe hyperkalemia

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Hyperkalemia, or elevated extracellular potassium ($[K]_o$) in acute myocardial ischemia, has the major effect on cell excitability by depolarizing resting membrane potential, causing reduction in sodium channel availability. In this study we considered velocity change in hyperkalemia both in computational modeling and optical mapping experiments on neonatal rat cells.The velocity appeared to change in biphasic way: in mild hyperkalemia ($[K]_o$10mM) it remains the same. Reasoning from the fact, that in severe hyperkalemia excitation waves are still able to propagate, but sodium channels are considered to be inactivated. Finally, we showed that in severe hyperkalemia excitation waves are able to propagate without available sodium channels using tetrodotoxin (TTX) to block them.

Dynamics of scroll wave filaments in personalized models of the left ventricle of the human heart

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We study the influence of geometrical features of the left ventricular (LV) anatomy on the dynamics of scroll wave filaments. We utilized echocardiographic images of the human heart to develop personalized LV models based on our analytical anatomical model of the LV of the human heart. Here we used 5 models for patients without pathology, 1 model for patient with dilated cardiomyopathy and 1 model for patient with ischemic heart disease. Myocardial electrophysiology was simulated by means of the Aliev-Panfilov model. We found that attractor position for the scroll wave filament depends essentially on the LV geometry remodelling. Supported by RSF #14-35-00005.

Deriving of macroscopic intracellular conductivity of deformed myocardium based on its microstructure

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The model of change of intracellular conductivity of a myocardium due to its deformation is developed. We first consider the case of stretching in material axes. The derivation of macro-conductivities was carried out on the basis of microstructural model of P.E.Hand, B.E.Griffith, and C.S.Peskin, where heart tissue is a periodic lattice of cells containing conducting fluid, and conductivity of gap-junctions was considered through boundary conditions on sides of these prisms. For this model the solution can be received analytically.

When deriving the dependence of conductivities on deformation we suppose that cytoplasm is isotropic electrolyte, conductivities of gap-junctions are constant and the deformation of cell is the same as for the whole tissue. Model was generalized for the general deformation where shifts in material axes are present. The analytical solution can be received in this case as well. This work was supported by RFBR, grant 14-01-96032, regional program "Ural".

Personalized 3D models and applications

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We present a state-of-the-art approach to the design of patient-specific models on the basis of MRI or CT data. At the preprocessing stage the segmentation of the medical image is applied. We discuss several methods of automated segmentation of vascular networks as well as a mathematical hemodynamic model based on the segmented data. One medical application is considered: the numerical assessment of the Fractional Flow Reserve in the coronary network. Vassilevski Yu. et al. Russian J. Numer. Anal. Math. Modelling, V.30, No.3, p.185-201, 2015 Danilov A. et al. Int.J.Numer.Meth.Biomed.Engng., e02754, 2015 Копылов Ф.Ю. и др. Терапевтический архив, Т.87, No.9, с.106-113, 2015 Gamilov T. et al. Russian J. Numer. Anal. Math. Modelling, Vol. 30, No. 5, pp. 269-276, 2015

First results of fully coupled 3D models of in-stent restenosis

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Computational modelling can lead to valuable insights into various processes involved in cardiovascular diseases and support clinical decision making. This work deals with modelling in-stent restenosis in a cylindrical 3D coronary vessel. For this purpose we use a fully coupled 3D multiscale model, which is based on an earlier 2D and preliminary 3D model and includes an agent-based submodel of the vessel wall and a lattice Boltzmann submodel of blood flow. The aim of this work is to reproduce results of the previous 2D model, but now for realistic 3D geometries, but more importantly, to demonstrate the capability of the 3D model to reproduce in-vivo data. For this purpose various stent deployment depths and two different reendothelialization scenarios are considered. We test these scenarios with two different stent geometries, which are based on real stents.

Biomechanics. Experimental and mathematical models

The ‘length-tension’ loop in isolated myocardial preparations of the right ventricle of normal and hypertrophied hearts of male rats

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To assess the influence of geometrical factors on cardiac contractility indexes of whole heart the mechanical activity of isolated thin trabeculae of the right ventricle of rats with and without myocardial hypertrophy contracting under physiological load conditions were investigated. Such contractions reproduce the succession of isometric and isotonic load in a single twitch, similar to the changes in pressure and in volume of the heart cavity during cardiac cycle. After monocrotaline injection of 2 month old rats, hypertrophy of the right ventricle was developed. For the first time shown, that the loop area ‘stress-strain’ in the hypertrophied myocardium revealed the increase compared with that in the myocardium of rats in the control group under the same afterload values. The angle of slope of end-systolic elastans ‘stress-strain’ decreased in the hypertrophied myocardium compared with control group rat myocardium. Results correlate with the change in the ‘pressure-volume’ loop.

Automatic control model of the three-tier arm type manipulator in the aimed-movement task

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In this work we consider the problem of constructing automatic control models of three-tier limb-type manipulator repeating flat goal directed human movement. Moreover, we assume that the geometrical limitations of the human hand were imposed on the manipulator. We consider the elbow and shoulder angles as parameters of the position. Wrist angle is fixed. The space of end angular positions was obtained analytically with respect of hand parameters and geometric restrictions. We constructed automatic control and estimated its performance. We recorded the natural motion of human hand and compared results with results of automatic control. As a result we derived the mathematical model of control of three-tier manipulator that is similar to manipulation model of real limb motion. The investigation supported by RSF grant 14-50-00029.

Mathematical modeling of dynamics of development of Parkinson's disease on the tremor parameters

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In the framework of the compartmentae-cluster approach there is possibility of constructing adequate mathematical models that may be of several types supposedly stationary modes of biomechanical systems. In the framework of the new theory of chaos and selforganization, when system state vector x=x(t)=const. The vector can occur within a bounded volume of the phase space of states. Introduced new criteria for the separation of these two types of motion (tremor and tepping) based on the paired comparisons matrix samples tremorogramm and teppingramm . Models of the evolution of the tremor in the mode of the three transitions: normal postural tremor, tremor in Parkinson's disease and the transition to a rigid form of the disease. A comparison of model data and observations on patients. Demonstrated specific examples of parameters matrix of paired comparisons and quasi-attractors while perturbation the final test.

Development of the biomechanical approach to tooth movement under the orthodontic treatment

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Problem of orthodontic tooth treatment of dentoalveolar anomalies is investigated. As a part of this work, biomechanical approach to tooth movement is suggested. For the considered system "tooth-periodontium", the model of rigid body partly emerged in linear-elastic medium is used. Tooth executes an initial movement under the action of applied force system. The approach is based on the well known concept "center of resistance of tooth" (which has properties analogous to the center of mass of free body) and new one of "region of resistance of tooth", introduced by authors. It is the generalization of concept "center of resistance". Properties, conditions of existence, types of new object are researched. It is stated and solved the optimization problem of orthodontic tooth displacement under the applied force system, which is not violate the physiological normes of the surrounding tissues of tooth.

Reaction-diffusion waves in mathematical model of blood coagulation

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The work is devoted to mathematical modeling of blood coagulation. In case of vessel damage proteolytic enzymatic cascade is launched resulting in formation of fibrin clot on the injury site. Kinetics of clot formation is determined by the distribution of thrombin concentration in blood flow. Any alternations in thrombin formation lead to serious physiological aggravations. Propagating from the injury site with constant speed, thrombin

formation can be described as a reaction-diffusion wave. We consider a mathematical model of the coagulation cascade and study existence, stability and speed of propagation of its traveling wave solutions. We propose an analytical estimate of the speed of thrombin wave propagation using narrow reaction zone method developed in combustion theory. Using this method we also derive conditions on the thrombin inhibitor concentrations that can prevent clot growth and compare the obtained estimates both with more complex models and available experimental data.

Mathematical modeling of alveolar ventilation and gas exchange during treadmill stress tests

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Physiological tests with incremental or ramp protocols are the most common methods of estimation the level of aerobic capacity. A cardiorespiratory system is one of limiting factors of athlete performance. The increase in gas exchange can be achieved either by increasing the frequency of the respiratory cycles, or by increasing the tidal volume. However, at higher frequencies above a certain level, there is a noticeable drop in the efficiency of O2 delivery and CO2 removal. In this work the method of numerical simulation of alveolar ventilation and muscle gas exchange kinetics taking into account the individual topology trachea-bronchial tree (based on MRI data) of the athlete and using the experimental data of O2 uptake and CO2 are proposed. This model can be used to estimate the body exercise tolerance in terms of efficiency of gas exchange in the lungs, to determine the body response to different types of work rate intensity and to investigate respiratory patterns.

Strain prediction in 3D finite element models of cardiac mechanics

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We present a new model of cardiac mechanics to predict strain in the ventricular wall in normal and disease hearts using idealistic ventricular geometries as well as high-resolution finite element meshes that accurately reflect complex anatomical features. The model predicts the global characteristics of ventricular contraction and strain in the ventricular walls for different hemodynamic conditions, contractility levels and pacing protocols. To demonstrate the model capabilities, we simulate and compare with clinical data several conditions including decreased stressed blood volume, aortic stenosis, reduced contractility and abnormal ventricular activation.

Simulation of digestion processes in antroduodenum: food particles dissolution in consideration of functional disorders

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A submodel of multiphase flow in antroduodenum is developed within the framework of multiscale model predicting the evolution of human functional disorders under environment influence. Mathematical formulation of the problem is written taking into account chemical and enzymatic reactions, particles dissolution, absorption of chemical substances, secretion and motor functions of digestive tract. 3D antroduodenal form and characteristics of motor activity are obtained from ultrasonography. Some results such as food particles dissolution rate, acidity of stomach and intestine content, characteristics of gastric emptying are analyzed in consideration of functional disorders. The reported study was funded by RFBR according to the research project № 16-01-00126 A.

Load-dependence of the electromechanical function of myocardium in a 1D tissue model

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Regional heterogeneity in the electrical and mechanical function of myocardium may contribute to its contractile function. Here we study effects of interaction between cardiomyocytes in a 1D model of myocardial tissue. We simulate physiological mode of cardiac muscle contractions under various mechanical load. Local deformations in the model depend essentially on the activation sequence and the mechanical load applied, creating gradients in the electromechanical properties of cardiomyocytes and affecting overall muscle output. Supported by RAS Program I.33P.

Transmural gradient in mechanical properties of isolated subendocardial and subepicardial cardiomyocytes

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Myocardial heterogeneity is an intrinsic property of the normal heart, and becomes more prominent in pathological conditions. Despite the large amount of experimental evidence for the presence of transmural heterogeneity in the electrophysiological properties of cardiomyocytes, much less is known about the heterogeneity in the mechanical function of these cells and the underlying mechanisms of excitation-contraction coupling. In the present study we investigate the differences in mechanical properties of isolated subendocardial (ENDO) and subepicardial (EPI) cardiomyocytes of mouse left ventricular wall at different preloads using our recently developed single cell stretch method (Iribe et al., 2014). Then we used our electromechanical

ENDO and EPI models (Khokhlova et al., 2015) to integrate the experimental findings into our cardiomyocyte models and to predict underlying cellular mechanisms. Supported by RFBR (16-31-60015, 14-01-00885), Program RAS I.33П and JSPS KAKENHI 2628212.

Optimal control problem and indexes of stabilometric "test with the visual step input"

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Models of the motion of person who undergoes the stabilometric "test with visual step input" are considered. At the beginnings of the test person stand on the stabilometric force plate. Center of pressure (COP) image and target are displayed on the screen in front of the person. Center of target is superposed with the mean COP position on the basic plane. During test the target changes position jump-like and the person's asked to change quickly his ankle angle to superpose COP image with the center of a target on the screen and to hold it hereafter in target region. For test results analyses it is suggested to use the solution of optimal control of position of the inverted pendulum with actuator in a pivot. The speed-of-response control and LQ stabilization optimal problems are considered. Possibility of usage of optimal solutions for generation of test indexes is discussed. This study was supported by RSF grant 14-50-00029.

A study of the edge segments of saccadic eye trajectory

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Saccadic movement (SM) is a fast eye movement, with eye speed up to 800°/s. Saccades are divided into induced, which were provoked by some stimulus, and arbitrary, the beginning of which was not preceded by any special incentive. In most cases, exceeding of a certain velocity and/or displacement threshold is considered as a start criteria of SM. In terms of mechanic, none of these criteria give the answer to the question: when the SM starts. Each of them detects that the movement has already begun, and it is fast, but don't catch the initial, presaccadic phase. Although the end of the SM in most cases is believed to be connected with the transition to stabilization of gaze, another type of eye movement. Due to the asymmetry of the criteria, only smooth SM and SM with postsaccadic elements are commonly studied. The report will consider the records of SM and attempt to analyze the beginning and end of the SM in terms of mechanic. The investigation supported by RSF grant 14-50-00029.

Load-dependence of intramyocardial slow force response in heterogeneous myocardium

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We used mathematical models to study the intramyocardial slow force response (SFR), caused by internal mechanical interactions of muscle segments in heterogeneous myocardium [1]. We simulated afterloaded contractions of a pair (duplex) of end-to-end connected functionally heterogeneous virtual muscles. The intramyocardial SFR is expressed in gradual changes in the overall duplex shortening and in the individual contractility of each coupled muscle. The mechanical responses are accompanied with slow and opposite changes in the shape and duration of both the action potential and Ca^{2+} transient in the cardiomyocytes of interacting muscles. We found that the contractility changes in interacting muscles follow the alterations in the sarcoplasmic reticulum loading in cardiomyocytes which result from the length-dependent Ca^{2+} activation of myofilaments and intracellular mechano-electrical feedback. Supported by the RBRF (#14-01-00885) and RAS Program I.33P. 1. Markhasin et al., PBMB, 2012.

Experimental study of the intramyocardial slow force response

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We performed a series of experiments on cardiac muscle duplexes to verify predictions of the mathematical models on the load-dependence of intramyocardial slow force response in heterogeneous myocardium. Muscle duplexes were formed of two thin trabeculae of a right ventricle of the Wistar rat heart. Interactions between end-to-end connected muscles were simulated by means of a hardware-software complex developed by us earlier. The experimental setup was improved to study mechanical activity of the separate or coupled muscles in the isotonic mode of contractions. It was shown that the time course and the magnitude of contractions of each muscle changed slowly cycle-by-cycle after muscle coupling and duplex disconnection, reflecting effects of muscle mechanical interaction on their contractility. To evaluate the load-dependence of the muscle response to interaction we used the force-velocity relations. Results obtained in physiological experiments were in good agreement with model predictions. Supported by the RBRF (#14-01-00885).

The mechanics of a discrete multi-cellular model of arterial in-stent restenosis

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The local dynamics of in-stent restenosis in coronary arteries is determined by the level of wall shear stress acting on injured vascular endothelium due to blood flow. Nevertheless, realistic simulation of the mechanics of an arterial wall (and especially of tunica media) is necessary to model the actual configuration of the lumen at stent deployment and at further smooth muscle cells proliferation. We consider a 3D anisotropic discrete tissue model

composed of spherical cells in a dense hexagonal pack. Several cell-center interaction potentials for repulsion and attraction are studied, including: linear springs, Hertz contact model and its Neo-Hookean extension, Johnson-Kendall-Roberts model of adhesive contact. Numerical simulations of uni-axial tension tests on strips of tunica media are presented here. The obtained stress-stretch curves are compared to the in-vitro results. The influence of cell interaction potentials on the stiffness characteristics of the tissue is discussed.

Modelling of soft tissue deformation for static elastometry

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Physical, numerical and finite-element models of deformation are developed for a soft tissue with inhomogeneity taking into account elastic moduli and densities of tissue and inhomogeneity, static pressure applied, and also the shape, size and depth of inhomogeneity. Proposed models allows to solve the inverse problem of quantitative (not only qualitative) estimation of soft tissue, internal organs (e.g., liver) and tumors mechanical properties based on the measurement of deformation and pressure during compression. The static elastography method currently used offers the possibility to obtain 2D images of shear modulus field in relative units. Implementation of proposed models in conjunction with developed device for measuring the pressure during compression allows to perform the elastometry (in Pa units) of a soft tissue with inhomogeneity selected area using a typical ultrasonic diagnostic equipment operating in B-mode and having a function for linear dimensions measuring.

Occlusion correction based on biomechanical modelling

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The method of occlusion correction existing in dental practice at quantitative restrictions on values of stresses into the temporomandibular joint disc and the mandible is verified based on formulation and solution of the control problem. The problem allows us to determine specific values of control parameters within ranges of these normal values. The problem of the stress-strain state of the mandible and the temporomandibular joint disc is formulated for the accounting these restrictions. It lies in the fact that stress ratios should not exceed specified limits. Set of muscle involvement coefficients (minimax values of relations of muscle efforts to their maximal values) is determined at solving of above-mentioned problems for normal values of parameters characterizing occlusion. Each set of values of occlusion parameters corresponds to specific value of this coefficient. Minimal value of this coefficient is interested. It indicates case of more equal stress of muscles as possible.

Development of the “Virtual physiological human” concept

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Development of medicine in the XXI century rests on four directions started from letter “p”: predictive medicine, personalized medicine, prophylactic medicine, participatory medicine (patient is a participant of treatment process). One from perspective advantage in this direction is development of International project “Virtual Physiological Human”. According to this conception, human organism is considered as a complex multiunit biomechanical system. In this research, we pay special attention to analysis of structure and physiological peculiarities of the maxillofacial system of human in dynamics of its development, beginning from birth and further during all human life. Very important object from point of view of biomechanics and relations with other systems of organism is a pair of temporomandibular joints. We conduct analysis of relation of pathologies in the maxillofacial system and disturbances of intracerebral blood circulation including insult to the brain.

3D FEA simulation of the proximal human femur

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The work is dedicated to medical problem which covers the improvement of individual surgical tactics treatment of the femoral neck. Osteosynthesis with three screw fixators is a traditional method of treatment of this injury. The proportion of nonunion is about 20-25% because of the stress and as a result bone resorption. In 2005-2011 new technology of controlled osteosynthesis was developed where the volume of tightening fixators torque is calculated for each patient. However, existing biomechanical models don't take into account the exact shape of the patient's proximal femur and the spatial distribution of mechanical properties of bone. The aim of this paper is to create a FEA model of the proximal femur. The stress-strain state of the bone during walking in normal conditions and after the installation of fixators was investigated by using processing package Ansys. The results of the research allowed to determine the initial parameters for adaptation process modeling.

Modelling viscoelastic hysteresis of passive myocardial sample

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In this study we analyse experimental data on the viscoelastic hysteresis of isolated rat myocardium in a passive state in saline, calcium-free solution and after sodium dodecyl sulfate (SDS) treatment performed. The frequency range of the hysteresis has been selected from 0.1 Hz to 10 Hz. It is showed a statistically significant decrease in force amplitude at 30% during the length cyclical changes of the preparation after SDS treatment. It is found that the hysteresis loop area increases with increasing frequency. Numerical experiments were performed in the framework of the model of morphofunctional unit developed by us earlier. It is shown that the model adequately reproduces the experimental

viscoelastic data for hysteresis in the whole range of frequencies investigated in saline and in calcium-free solution. Thus, under the proposed model approach the contribution of the structural components into resulting myocardial viscoelastic characteristic can be defined.

Mathematical modeling of the left atria mechanical action with mitral regurgitation

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The aim of research is computational investigation of the stress-strain state problem of the left atrium with the help of ANSYS computer program. 3D-models of the normal left atrium and pathological left atrium with mitral regurgitation were built in ANSYS computer program. Numerical solution is obtained for Mooney-Rivlin potential. Deformation features of the left atrium, which based on analysis of the results, are found in normal state and pathology. The stress-strain state problem was solved numerically in the framework of the spatial nonlinear theory of elasticity. The obtaining of the experimental data of mechanics of left atrium was carried out in the Center of Cardiac and Vascular Surgery in Perm. There are forty radiopaque markers on the outer side of the walls that visible with computer tomography. Then the left atrium is pumped physiological solution to keeping of pressure from 2 to 16 mm Hg.

Accuracy of 1D blood flow simulations in relation to level of detail of the arterial tree model

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1D models are widely used for simulation of arterial hemodynamics without hard demand for computational resources. The accuracy of such models is well-studied and estimated by direct comparison with results of full 3D simulation on the equivalent geometries and with in-vivo measurements. With the availability of very detailed full body anatomical atlases we can create 1D models with unprecedented levels of refinement. Since the personalization of such detailed models is challenging, the question about precision required for reliable 1D simulations in the major arteries can be formulated. The study of relation between accuracy of arterial geometry and results of simulation is presented here. The dynamics of pressure and flux in major arteries for arterial models of three various levels of detail were compared. The influence of various peripheral parts of arterial network on the accuracy and the role of boundary conditions are considered.

Mathematical modelling of airflow in human respiratory tract

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Mathematical model of "meso-level" of human respiratory system is developed as a part of multilevel model for evolution of functional disorders in human body, caused by environmental factors. The mathematical model of respiratory system consists of three connected submodels describing breathing process as set of synchronized processes of elastic deformations, gas dynamics, and diffusion. The results of inhalation and exhalation airflow in human respiratory tract received with the use of the ANSYS Fluent are presented.

Influence of artificial initial and boundary conditions in biomechanical models of blood vessels

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By numerical investigation of the dynamical behavior of blood vessels it is usual to consider a part of the vessel instead of the whole system and a problem in which the time changes within a finite interval instead of the pulsing process. This approach leads to some artificial boundaries and initial points which can affect the accuracy of a biomechanical model. The aim of this study is to investigate the influence of these factors analytically on the basis of a geometrically simplified model of circular cylindrical elastic shell containing viscous fluid. The asymptotic methods developed for non-biological elastic shells are modified for the biomechanical problem. It is shown that for the low-frequency vibrations which are characteristic for blood vessels the classical model of thin elastic shell can be reduced to a simplified one. Then the series of problem with different variants of boundary and initial conditions are solved and the differences between the solutions are outlined.

Electrophysiology. Experimental and computational models. Clinical studies

Arrhythmia modelling in tissue culture

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We use cardiac tissue engineering for experimental modelling of cardiac arrhythmia, based on rotating excitation waves, or re-entry. This model enables visualization of excitation waves using potential sensitive and Ca^{2+}-sensitive dyes, similar to experiments with real heart tissue, but with a much lower internal complexity. We present our recent results in patterning cardiomyocyte tissue culture and controlling its excitability. Among them are: the termination of spiral waves by pacing-induced drift and their forced collision with a boundary, conversion of the “anatomical reentry” (pinned spiral wave) to the “functional reentry” (free rotating wave), perturbation of a stably rotating spiral wave by decreasing the excitability of the system with time. We also propose a method to control the excitability of cardiomyocyte layers by means of adding of photo-reactive substances, azoTAB and c-TAB.

Pharmacological analysis of transmembrane action potential's morphology of myoepitelial cells in the spontaneously beating heart of ascidia Styela rustica

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Heart of tunicates has two centers of pacemakering, which initiate the rhythm of heartbeats alternately. Mechanisms of action potential (AP) generation in the pacemaker cells, localized at both ends of the tubular heart, are still unknown. We present the results of the study of the currents blockers (4-AP, TEA, ivabradine, lidocaine, nifedipine) on AP morphology of spontaneously beating ascidia heart. The heart (n=23) was isolated and pericardium was relived. APs were recorded with glass microelectrodes in bath with sea water. All isolated hearts exhibited with bursts as episodes from 11 up to 30 APs (19±6 impulses and with a frequency in a pack of 16±2 beats per min (bpm, at 15 °C, excluding pauses of silence). The change of the leading automaticity center occurred after a pause of about 30 s. So, on the basis of our results and data of literature we conclude that the IK and If currents plays a key role in the generation of automaticity in the myoepitelial heart cells of the ascidia.

The crucial role of the rapidly activating component of outward delayed rectifier K-current (IKr) in pig sinoauricular node (SAN)

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IK is largely attributed to the rapidly activating component of IK (IKr) in rabbit SAN cells (Ito, Ono, 1995; Verheijck et al., 1995), whereas the slowly activating component of IK (IKs) is a major component in guinea-pig (Matsuura et al., 2002) and porcine SAN cells (Ono et

al., 2000). We use suppose that the role of IKr and IKs in forming the spontaneous APs may differ depending on the species and heart rate. We studied this hypothesis. In the control solution the frequency of APs generation in SAN of pig and mouse were correspondingly 48±5 (beat per min, bpm) and 289±11 bpm. Selective blocker E4031(1 mkM) for IKr decreased the frequency of generation of spontaneous APs in SAN of rabbit, guinea pigs, mouse, and pigs accordingly at 26, 27, 28 and 31% compare to the control. Thus, the obtained data suggest that the contribution of IKr to the formation of APs does not depend on frequency of heart beat, and IKr is a major component in pig SAN cells.

Numerical methods for electrocardiography modelling

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Electrocardiography (ECG) is widely used as diagnose techniques in medical clinics. The numerical modelling of the underlying physical processes may be used to improve these medical techniques. Numerical modelling is used to solve the forward problem of electric potential distribution. In order to solve the underlying differential equations one should perform several steps. The Visible Human Project data were used to perform semi-automatic image segmentation with ITK-SNAP software (itksnap.org). An anatomical human model was reconstructed from segmented image and an unstructured mesh was generated using CGAL Mesh library (www.cgal.org). The differential equations were solved using finite element method with P1 elements using Ani3D library (sf.net/p/ani3d). Several numerical experiments were performed. Acknowledgments: The research was supported by Russian Federation President Grant for Government Support of Young Russian Scientists MK–7839.2015.1

The electrical resistivity of a segment of the tail, lungs, liver, intercostal muscles of grass snakes during cooling

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Electrical impedance allows to assess the influence of temperature on blood distribution in humans (Cai et al., 2000). The relationship between temperature and electrical impedance of organs and tissues for endotherms and ectotherms (Lingwood et al., 2004; Nicolaev, 1990) were determined. The study investigated the electrical conductivity of the snake's body at temperature changing from 27 to 3°C. The electrical impedance measurements were made on anaesthetized grass snakes at 150-10kHz, on the tail, lungs, liver, muscles. The phase recorded on the tail significantly increased. The electrical resistance of the tail segment and muscles showed a tendency to increase during cooling. A significant decrease in the electrical resistance of lungs was revealed when cooling the body from 25±2°C to 21±3°C; there was a significant decrease in the electrical impedance of the liver when cooling the body from 23±1°C to 17±2°C and to 12±4°C that could indicate a redistribution of blood flow to them.

Role of TRPC1 channels in the propagation of electrical excitation in the isolated rat heart

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Role of transient receptor potential cation channels member 1 (TRPC1) in the heart today poorly understood but it is a large scientific interest. TRPC1 selectivity for calcium ions and the ability to activate them on a store-dependent manner and in response to the mechanical action suggests the possibility of their participation in the development of heart disease (that is already confirmed by some studies). The aim of our work is to establish the dependence of the propagation velocity of the electric excitation in the heart on the activity of TRPC1 channels. In order to achieve the task registration of the electrical activity of isolated rat heart perfused by Langendorff method was held with using of multi-electrode flexible arrays.

Ventricular lead position and mechanical dyssynchrony in response to cardiac resynchronization therapy

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The aim of retrospective study was to evaluate the influence of baseline left ventricular (LV) mechanical dyssynchrony and ventricular leads location on long-term outcome in 40 patients with cardiac resynchronization therapy (CRT) divided into 2 groups with high/low response to CRT. Ventricular lead position was assessed using ECG vector analysis during the isolated left/right ventricular pacing according to the 12 LV and 3 right ventricle segments. Mechanical dyssynchrony was evaluated with tissue Doppler imaging using the same segments. Results: ischemic cardiomyopathy prevailed in Group II. Number of baseline mechanical dyssynchrony zones was bigger in Group I. Overlap of LV lead location and the latest mechanical LV zone was higher in Group I. Interlead distance and placing the LV lead concordant with the site of the latest mechanical LV zone positively correlated with high response to CRT. Mechanical dyssynchrony and interlead location can be predictors of the response to CRT.

Stochastics and chaotic analysis of electromyogram and electroencefalogramm

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It was demonstrated the feasibility of applying the method of multi-dimensional phase space as a quantitative measure for the evaluation of chaotic dynamics on the example of the electromyogram (EMG) and electroencefalogramm (EEG). The investigation use the method of multi-dimensional phase space. In the study and modeling of complex biological objects there is the possibility of introducing traditional physical methods in biological research and new methods based on theory chaos and self-organization. As a measure of the state of the EMG and EEG of the person (weak muscle tension and strong) used quasi-attractors volumes of multidimensional phase space. It provide the identification of the actual

measurements of the parameters of the functional state with weak muscles (F1=5 daN) and strong static (F2=10 daN) stress and human brain. Was built timebase signal obtained with myograph and were built autocorrelation function A(t) of EMG and EEG.

New insights into the pacemaker and conduction system cells organization in the adult avian heart

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Previous histological studies showed that in addition to a sinus node, an atrioventricular (AV) node, an AV bundle, left and right bundle branches birds also possess a right AV ring of Purkinje fibers that is located in the atrial sheet of the right muscular AV valve. In this work, we studied the topology of pacemaker myocytes in the atrial side of the isolated chicken and pigeon spontaneously contracting muscular AV valve using the method of microelectrode mapping of action potentials (APs). We show that AV cells having the ability to show pacemaking reside in the right AV valve. Pacemaker APs were exclusively recorded close to the base of the valve (where annulus fibrosus runs) along its whole length from dorsal to the ventral attachment to the interventricular septum. These APs have much slower rate of depolarization, lower amplitude, and higher diastolic depolarization than APs of Purkinje (conducting) cells. We conclude the right AV valve has a ring of pacemaker cells (but not Purkinje cells) in the avian heart. This study was supported by the RFBR.

Cardioelectric field in rats with experimental pulmonary hypertension during ventricular depolarization

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The spatial and amplitude-temporal parameters of the cardioelectric field have been studied on the body surface of female Wistar rats with experimentally induced pulmonary hypertension during ventricular depolarization. Cardioelectrical potentials were recorded from 64 subcutaneous electrodes uniformly distributed around the animal chest before and 4 weeks after a single injection of monocrotaline (60 mg/kg body wt, sub/q). In rats with experimental pulmonary hypertension, on the cardioelectric field on the body surface a significant increase of amplitude (a value of maximum and minimum extrema) and temporal (the duration of the first and second inversions, total depolarization duration) characteristics occurred compared to the control.

Simulation of the fibroblasts effect on synchronization and rhythmogenesis in the sinoatrial node

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We have developed a model of the sinoatrial node (SAN) tissue incorporating cardiomyocytes interacting with the fibroblasts via the gap junctions. Simulations revealed almost no effect of fibroblasts on the established period of the SAN oscillations. However, fibroblasts affected the number of leading centers and their location (here we define the leading center as the cell that depolarized earlier then then its surrounding cells within the range of 210 μm). Thus, after 50 s of simulations, we observed 12 leading centers located from 2.3 to 3.4 mm from the center of the tissue, but only 2 leading centers located from 0.4 to 0.7 mm from the center of the tissue in the presence of the fibroblasts. Simulations of ACh superfusion in the presence of fibroblasts resulted in sinus pause up to 2 seconds.

Cooperation of membrane and calcium oscillators in sinoatrial node cells

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Stable Ca^{2+} oscillatory dynamics in cardiac pacemaker cells (CPC) is developed due to a synergetic effect of the coupling of the classic sarcolemmal voltage oscillator (“membrane” clock) and the intracellular calcium oscillator ("Ca^{2+} -clock"), whose functioning is governed by the ryanodine (RyR) channel gating. We developed an integrative model of coupled oscillators using a simple electron-conformational theory to describe the stochastic RyR gating in a Ca^{2+} release unit (RU). We show that the coupling can provide a stable action potential generation in CPCs, however, with clear signatures of “micro-arrhythmia”, the fluctuations of the frequency and amplitude of the Ca^{2+} release. We studied the effect of “funny” current and of the RyRs’ sensitivity to the [CaSR] and [CaSS] on the behavior of the Ca^{2+} RU. Depending on the model parameters either the membrane or Ca^{2+}-clock plays the master role providing the astonishing stability of the auto-oscillatory regime. Supp. RSF 14-35-00005.

Experimental and computational models in immunology

Systems approach to modelling the "virus-host organism" interaction in infectious diseases

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Virus infections in humans are characterized by a broad spectrum of the course and outcomes ranging from acute to chronic and lethal variants. Experimental and clinical studies of the pathogenesis of virus infections are based on the use of the high-throughput technologies for quantitative characterization of the system behavior at the molecular-, cellular-, tissue and systemic levels of regulation. Understanding of the multilayer regulatory mechanisms underlying the observed spectrum of the dynamics of infectious and the response to antiviral and immunomodulatory therapies represents a fundamental task requiring the application of systems approaches for their mathematical modelling. The infection is viewed as a trajectory of a dynamical system in the state space of the quantifiable characteristics of disease. The unfavorable course of infection is interpreted as abnormal systems dynamics. Some key issues and recent results in the development of integrative mathematical models of immune responses to experimental and human infections, such as LCMV and HIV are presented. The study is supported by the Russian Science Foundation Grant 15-11-00029.

Impact of immobilization stress on change of protein fractions hemoglobin of bone marrow in rats

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Currently, the issue of changing the protein fractions of hemoglobin bone marrow (BM) and their role in the adaptation of the organism under stress is not fully understood. In this context, the aim of work was to study changes in protein fractions of hemoglobin BM rats under immobilization stress. Immobilization was performed according to the method H.Selye, 1965. Performance analysis was conducted after 6 hours and 2 days after the end of exposure. It's found that the stress response results in bone marrow cells to enter the bloodstream and a decrease in hemoglobin the BM on the 2 day. In this case at all stages the 1 and 2 of the protein fractions decrease on the background of the increase – 3, 4 and 6 isoforms. This indicates the production of new cells in BM and activation of erythropoiesis.

The features of biochemical properties of extracellular matrix of bone marrow in rats in conditions which stimulate granulocytopoiesis

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Contact cells with the extracellular matrix (ECM) affects their proliferation, differentiation and metabolism. It is believed that there is an optimum composition of ECM for each class of hematopoietic cells. In this connection, we examined the biochemical composition myelokaryocytes and ECM in inflammation. Chemical parameters were

determined after 6 h and on day 2 after exposure. The low level of protein, urea and triglycerides are indicated in ECM at all stages after stimulation granulocytopoiesis, but at an early period to accumulate glucose and phosphorus, and later – calcium (Ca). Myelokaryocytes at early period characterized by reduced levels of urea, Ca and phosphorus, and later - enhanced enzymatic activity. Perhaps the nature of the observed changes reflect the particular metabolism of certain germs hematopoiesis. The concentration of glucose, Ca and phosphorus in the ECM can be one of the factors to maintain cells at various stages granulocytopoiesis.

A mathematical model of the functioning and mutual regulation of the immune and neuroendocrine systems in response to viral exposure under the impact of environmental factors, taking into account the evolution of synthetic function impairment

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Technogenic chemical factors have a negative impact on human body on the whole, and in particular the immune and neuroendocrine systems functioning and regulation. This paper considers a development of mathematical model of the immune and neuroendocrine systems interaction under viral infection. The model takes into account the synthetic function impairment when exposed to negative factors entering the body from the environment. A structural scheme of the model consists of a set of interconnected immune and endocrine systems elements, which take part in the body response to viral invasion. The mathematical model of regulation mechanism involving immune and endocrine systems elements is described using an equation system of 17 first-order ordinary differential equations with delay. Parameter identification is made based on the data describing the process of infection of the body with influenza virus. The reported study was supported by RFBR, research project No. №16-31-00333 мол_а.

The role of mast cells in the regulation of repair testicles

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It is supposed that tissues with different degree of immunological privileges have a lot of distinctions in processes of reparation. It can be connected with the mast cells excreting a wide range of biologically active substances and playing an important role in regulation the tissue repair. In this work results of morphometric researches of quantity and functional activity of mast cells in a testicle are presented. It is shown that in a testicle after damage the index of degranulation of mast cells increases in the absence of their expressed migration. Stabilization of membranes of mast cells promotes reparative regeneration of a testicle, on what specify growth of number of the normal spermatogones which are a proliferative pool for all subsequent stages of a spermatogenesis and considerable decrease in number of nonfunctioning tubules. Thus, quantity and a functional condition of mast cells have impact on the course of the reparative of processes in tissues with immunological privileges.

Simulation of immune processes using Bio-Medical Software Package

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The report presents Bio-Medical Software Package. We have written a program to simulate immune processes with different parameters. We also developed special control sections that allow having an effect on the system. The system is often described by delay differential equations (DDE). They are generalization of ordinary differential equations and arise in many areas of science: the control theory, mechanics, physics and economics. Furthermore, they can be used in immunology. Because most DDEs don't have analytical solutions, it is necessary to use numerical methods. Most existing application suites for DDE simulation are implemented with unfriendly user interface. They often require high-level knowledge about programming. To solve this problem we developed user-friendly package with maximum performance and sufficient flexibility. Bio Medical Software Package can be efficiently used in practical work and education.

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Modelling of t cell extravasation into a lymph node: from morphological basics towards clonal selection theory

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A hypothesis regarding a permanent recirculation of immunocompetent cells is based on central and peripheral organs of immunosurveillance. It was reported that in human 0.3x1011 T cells/day go through every lymph node (LN) (size: 0.5 – 0.8 cm). The data contain, however, certain controversies. If each T cell clone consists of only one cell, then the total amount of clones would be exactly 0.6x1011, which is much lower than the current estimates predicting diversity of TCR variants. Nonetheless, even if 0.3x1011 T cells would pass through LN within 24hrs it implies that ~350,000 T cells/sec undergo extravasation suggesting that during a 1min-transmigration HEVs are filled with very high amount of cells. However, even a preliminary analysis showed that the main factor resulting in quite a large amount of T cells migrating every second through HEV would be a very high number of T cell clones envisaged by a clonal selection theory.

Oral and maxillofacial manifestations of primary immunodeficiency syndroms

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According to data of russian and international physicians and scientists, the prevalence of primary immunodeficiencies is much higher than previously thought, and is about 2% of the population. Early diagnosis and treatment of these diseases will reduce mortality, infectious, oncology, autoimmune diseases. Among the signs of primary immunodeficiency diseases are malformations, which are traditionally associated with other congenital diseases. We performed research to assess the combination of various

malformations and primary immunodeficiency. These anomalies of the maxillofacial area are recommended as signs for targeted search of primary immunodeficiencies and other symptoms combined with them. For the doctors of different specialties one of the symptoms suggestive of abnormalities of the immune system should be abnormality of the maxillofacial development. It is one of the symptoms for studying patients on the primary immunodeficiencies.

Evaluation of probabilities of antigen recognition by T-lymphocytes in the lymph node: a mathematical model

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Modelling of this process is an important task in terms of assessing one of the key provisions of the clonal-selection theory: all clones of T-lymphocytes must pass through each lymph node for effective recognition and the subsequent elimination of the antigen in a short time. The number of T-lymphocyte clones postulated in this theory (10^{17} - 10^{19}) is too much. The method of geometric determining of the probability was used to create the model. The simulation assumed that the antigen is associated with presenting cells. The analysis was performed in accordance with parameters: size, number and velocity of the interacting cells, size of the lymph node and time of recognition. In that case the effective detection volume of each clone must be $6*10^5$ cells for the total number of clones $6*10^{10}$ — the total number of circulating cells equal to $3*10^{16}$. This result also exceeds the total number of all cells in the body and confirms the assumption of clonal-selection theory imperfection.

Molecular basis of biological motility

Mutations in the central part of tropomyosin molecule affect the actomyosin interaction

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Functional effects of point mutations in tropomyosin (Tm) molecule stabilizing its central part on actomyosin interaction was studied with isolated sarcomeric proteins and at single molecule level with an in vitro motility assay and an optical trap. It was found that myosin step size, its duration and force of single interaction of myosin molecule with thin filament containing any of studied mutants are reduced with respect to WT Tm. Sliding velocity of regulated thin filaments in the motility assay and force of the interaction rose with the extend of stabilization of the Tm central part (Matyushenko et al., FEBS J. 2014). Surface density of myosin needed thin filaments to achieve half-maximal velocity is 2-fold and ~20-fold lower with single and double mutants, respectively, compared to WT Tm. These data well correlate with bending stiffness of thin filaments containing Tm mutants measured with the optical trap (Nabiev et al., Biophys. J., 2015). Supported by RFBR grant 13-04-40101-N.

Functional studies of tropomyosin mutations associated with dilated and hypertrophic cardiomyopathy

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The inherited hypertrophic cardiomyopathy (HCM) and dilated cardiomyopathy (DCM) can be caused by missense mutations in the TPM1 gene encoding α-tropomyosin (Tpm). We studied the effect of DCM (E40K, E54K) and HCM (E180G, D175L) mutations of the α-Tmp molecule on calcium regulation of acto-myosin interaction using an in vitro motility assay and an optical trap. In the in vitro motility assay mutation E40K decreased the maximal sliding velocity of the reconstructed thin filaments over myosin coated surface and its calcium sensitivity while HCM mutations increased both the velocity and the sensitivity. Mutation E54K did not affect the characteristics of pCa-velocity relation in the in vitro motility assay. The HCM and DCM mutations affect the characteristics of single myosin interaction with thin filament at saturating calcium concentration. The data may contribute to understanding the molecular mechanisms of the HCM and DCM genesis Supported by RFBR grants 15-34-20136, 15-04-01558.

The role of glutamate NMDA-receptor-NO synthase axis in the effect of 24-hydroxycholesterolon synaptic vesicle exocytosis at the mouse neuromuscular junctions

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Synaptic activity leads to a decrease in cholesterol availability due to conversion of cholesterol to 24-hydroxycholesterol (24HC).Using electrophysiological and optical methods we found that 24HC (0.4 mkM) potentiates evoked neurotransmission in the mouse neuromuscular junctionsowing to increases in both the amount of synaptic vesicle involved in exo-endocytosis and the rate of their recycling. In addition, our data indicate that effect of 24HC on vesicle exocytosis depends on activity of NMDA-receptor and NO synthase. We now propose that activation of postsynaptic NMDA-receptor -NO axis attenuates the exocytosis during strong activity, while 24HC acts as antagonist of this path by hindering the increase in NO. Since 24HC had the effect at low concentration in the muscles located far from endogenous sites of 24HC origin (brain), we speculate that brain-derived 24HC can regulate neuromuscular transmission, when its plasma level becomes more. Supported by RFBR16-34-00127/14-04-00094.

Increasing μ-calpain activity in striated muscles of alcohol-fed rats

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Role of μ-calpain (80 kDa) in development of atrophic changes in heart and m. soleus of alcohol-fed rats was studied. Using Western-blotting statistically significant increase (2 times) in content of autolytic fragments of μ-calpain (78 and 76 kDa) was revealed in m. soleus of alcohol-fed rats that indicates on increasing proteolytic activity of this protein. These changes resulted in development of atrophy (decrease of muscle weight relatively body weight) in m. soleus and statistically significant decrease (by 10%) of titin content. On the one hand, the obtained data indicate development of alcohol-induced pathological changes in skeletal rat muscle, but on the other hand, decrease (1,25 times) of total content of μ-calpain and increase (1,2 times) of calpastatin content (inhibitor of calpains) may be compensatory reaction for decreasing development of atrophic changes in this muscle. Significant changes in studied parameters in heart muscle of alcohol-fed rats were not revealed.

Study of biphasic tension rise in contracting muscle fiber during ramp stretch

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During ramp stretch of isometrically contracting muscle fiber, tension and stiffness rise differently. Tension at first grows up linearly and quickly and then at critical level (pc) the rise sharply slows down. Stiffness grows up gradually but quickly approaches its rigor level several milliseconds before pc. To understand what is the reason of this phenomenon, we stretched fast skinned rabbit muscle fibers by 5% of its length at the velocity of 1,7 %/ms and 0,45 %/ms at 3°C and 25°C and monitored sarcomere length. The results show that during fiber stretch, attached myosin heads pass from force-generating state to pre-power-stroke state and tension increases due to attachment of new heads. These de novo attached heads are unable to generate active force but contribute to the resistance of the stretch. We assume that the decrease in tension rise occurs when all myosin heads get in pre-power-stroke state which is mechanically weaker than the force-generating state.

The Ca^{2+} regulation of actin-myosin interaction in atrium and ventricle

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Cardiomyocyte of the mammalian heart contains the whole pattern of the isoforms of contractile and regulatory proteins. Expression of proteins is switched at changing of the conditions of heart functioning. We investigated the role of sarcomere protein isoforms in contractile function of atrial and ventricle myocardium. Characteristics of unitary interactions of myosin molecule with α-actin isoforms were measured with an optical trap. The role of α-actin and tropomyosin isoforms in Ca^{2+}-regulation of interaction of atrial and ventricle myosin isoforms with regulated thin filaments was studied in an in vitro motility assay. α-Actin isoforms did not affect the parameters of single molecule interactions of cardiac isomyosins with F-actin. But characteristics of Ca^{2+}-regulation of actin-myosin interaction did depend on isoforms of contractile and regulatory proteins.
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Measurements of the bending stiffness of reconstructed thin filament with the optical trap

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Molecule of tropomyosin (Tpm) contains several conservative noncanonical residues, particularly G126 and D137 in the central part, which destabilize its α-helical structure. Substitution of any of these residues and, especially, both of them for canonical ones, G126R or D137L stabilizes the molecule that is seen by a suppression of trypsinolysis and an increase in thermal stability as revealed by DSC. These substitutions also change the

functional properties of the regulated thin filaments in an in vitro motility assay. We studied effect of stabilizing substitutions on the mechanical properties of Tpm by measuring bending stiffness of reconstructed thin filaments containing either each one or both of these Tpm mutants in two-beam optical trap. The results were compared with the stiffness of thin filaments with control Tpm and F-actin. It was found that the stiffness of thin filament increases with the extend of Tpm stabilization. Supported by RFBR grant 13-04-40101-N.

Structural and functional studies of tropomyosin species with cardiomyopathic mutations in the area of tropomyosin-troponin contact

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Tropomyosin (Tm) is a key regulatory protein of striated muscle. Mutations of Tm between conservative residues Glu180 and Cys190 locate in troponin T–binding site of Tm and associated with hypertrophic cardiac myopathy (HCM; Thierfelder et al., Cell, 1994). We studied the novel mutations, E180V, L185R, I172T. The mutation E180V unlike E180G (Kremneva et al., Biophys J, 2004) increased the thermal stability of the C-terminal part of Tm molecule. It also significantly increased the Tdiss value of the Tm–F-actin complexes compared to WT Tm while E180G decreased it. Both novel Tm mutations increased calcium sensitivity of the velocity of reconstructed thin filaments in the in vitro motility assay. Thus, structural abnormalities in the region of Glu180–Cys190 of the Tm molecule may affect functional properties of Tm explain, at least partly, why these changes are associated with human heart diseases. Supported by RFBR grants 15-34-20136, 15-04-01558.

Nitric oxide in uloaded muscle: powerless guard of stability

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Experiments using rat hindlimb suspension - HS showed that total nNOS content is decreased during gravitational unloading. We also found a decrease of NO levels in rat soleus muscle after 2 weeks of unloading (Lomonosova et al., 2011). Functional unloading leads to destruction of cytoskeletal and contractile proteins due to the activity of calcium-dependent proteases calpains. Our experiments with administration of natural NO precursor L-arginine demonstrated prevention of calpain-dependent hydrolysis of cytoskeletal proteins during functional unloading. Functional unloading is known to reduce expression of the slow isoforms of myosin heavy chains (MyHC Iβ). The reduced expression of MyHC Iβ mRNA during unloading was accompanied with the increased activity of GSK3β (Lomonosova et al, 2015). During 7 day rat HS study we didn't find any reduction in the GSK3β negative phosphorylation and MyHC Iβ mRNA content in the L-arginine supplemented rats. We believe that reduced level of NO content during unloading may participate in the slow-to-fast myosin shift. The study was supported by the grant of the Russian Science Foundation #14-15-00358.

Spatiotemporal activity profiling of key myosin regulators in endothelial cells with regard to control of cell stiffness and barrier dysfunction

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Myosin II is the major molecular motor of endothelial cells (EC) involved in control of barrier function and cell stiffness. We investigated how 210 kDa myosin light chain kinase (MLCK) and RhoA-activated protein kinase (ROCK) cooperate in regulation of endothelial myosin and affect these EC properties. We found that MLCK and ROCK are responsible for 80% of EC myosin activity. EC barrier dysfunction correlates with increased MLCK activity supported by active ROCK through MLC phosphatase inhibition. Hence, inhibition of MLCK and ROCK appears a promising approach to fight vascular leakiness in disease. We obtained stiffness maps of live EC using atomic force microscopy and found that the cytoplasm Young modulus is about 170 kPa, whereas the nucleus is 3.5-10 times softer. Both MLCK and ROCK control EC cytoplasm stiffness but MLCK does not affect nucleus stiffness. Thus, MLCK and ROCK seem important players in transduction of mechanical signals in EC. Supported by RFBR grant 14-04-01813.

Smooth muscle titin forms aggregates with amyloid-like dye-binding properties

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Using electron microscopy and spectroscopic methods amyloid-like properties of smooth muscle titin (1.5 mDa) isolated from chicken gizzard were observed. It was shown by electron microscopic, that the titin formed amorphous aggregates in solution containing 0.15 M glycine-KOH, pH 7.0-7.5. The titin aggregates were capable of interacting with thioflavin T, resulting in an increase in fluorescence intensity of the dye. An interaction of titin aggregates with Congo red and absorption band shifts to the long-wavelength side were observed. These data indicate that the smooth muscle titin aggregates have amyloid-like properties. This conclusion is consistent with circular dichroism data that revealed the absence of alpha helical regions in the secondary structure of aggregated protein. This study was supported by the RFBR (project nos. 14-04-00283).

Medical bioinformatics

Homeostasis and the evolution of complex biological systems

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There is no strong definition of complexity (living system) according to deterministic or stochastic approaches. The 5 principles of organization of living systems were proved, and such systems appear to be a special systems of the third type (STT) in natural science. For these systems, it is impossible to determine the stationary state in form of dx/dt=0 or in the form of invariance of distribution function f(x) for samples acquired in a row of any component xi of the vector of states x(t) in m-dimensional phase space of states. At the same time the mixing property isn't met, the autocorrelation functions A(t) do not tend to zero if t→∞, Lyapunov constants can continuously change the sign. Such STT – complexity do not satisfy the condition of Glansdorff–Prigogine theorem, i.e. P - the rate of increase of entropy E isn't minimized near the point of maximum entropy E. The concept of quasi-attractors and their movement in phase space were proposed for description of STT.

Limit of applicability the theorem of Glansdorf-Prigogine in the describing homeostatic systems

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The speed of the evolution of υ(t) of different systems are different, but the mechanisms and quantitative patterns may be similar. We will have different speeds of evolution for different biological systems, but in any case, we should have a formal mathematical apparatus, which describes all these processes. Now for complex, multicomponent systems in which the dimension of the phase space of States is large m>>1, there is no integrative methods for calculating the speed of evolution in the framework of the theory developed by I. R. Prigogine and P. Glansdorff. Thermodynamic approach to evaluating the evolution has been effective for systems third type, in this case at the level of molecular systems it runs – has a famous theorem of I. R. Prigogine (Nobel prize for thermodynamics non-equilibrium systems). It was proved that the changing of functional system did not provide the changing registration signal is entropy E.

Electron-conformational transformations govern the temperature dependence of the RYR2 gating

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Temperature is one of the most important factors affecting all physiological processes, in particular, cardiac excitation-contraction coupling. There is a growing evidence that the thermosensitivity of the ryanodine receptors (RyRs) gating can be responsible for the temperature effects on cardiac contractility. Current models of temperature effects on ion channels gating are based on thermodynamics and hence cannot provide a molecular insight

on the origin of the temperature effects. Here we address a simple physically clear electron-conformational model to describe the RyR gating. Results of the computer modeling allowed us to reproduce successfully all the temperature effects observed for an isolated RyR gating in vitro under reducing the temperature: increase in Popen and without any significant effect on. Supported by RSF #14-35-00005.

Towards to the bio-computer: from serial von Neumann architecture to systolic computer system in one chip

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A further increase in performance of the modern processor architectures is constrained by a thermal barrier on electronic components. At the same time, there are problems of high computational complexity (eg, simulation of the bio-macromolecules), the solution of which requires the performance of the order of 10E+18 FLOPS. The situation becomes deadlocked, when it is required to resolve such problems in real time and at restrictions on equipment. The paper outlines possible approaches to the implementation of massively parallel data processing by means of specialized processor architectures. Data processing in such processors has similarities with the operation of biological objects. Systolic processor architectures that allow for the greatest possible performance for signal and image processing are considered in the paper. Besides results of the first stage of development the analog-to-digital processor performing intelligent high-precision measurements of weak signals (current of about 1 nA) are discussed.

Hybrid technology of cohort rate of conditional lifetime risk trend assessment

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In order to assess the quantitative value of the factors affecting the clinical outcome in epidemiological studies of non-infection diseases statistical methods of multiple regression are often used. A hybrid information technology may provide additional benefits due to combining an artificial neural network (ANN) with another widely used method – regression with binomial assessment functional. Conditional lifetime risk was the prediction value. ANN could be used as a generator of risk models. The efficiency of the new algorithm is demonstrated by the example of professional bone cancer mortality. The assessment functional allowed its application for network customization as well as for statistically correct model selection. Forced centering of input signals and assessment function regularization were used in order to improve the generalizing capacity. The new method proved to be stable and resulted in logical and adequate conclusions.

Analytical methods for diagnostics of cerebral aneurysms

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The human cerebral circulation system is an object of high complexity. Arterial aneurysm is one of the most often cerebrovascular disease. The danger of arterial aneurysm latent in the progression of disease. That's why timely diagnostics of cerebral aneurysms is important medicine problem. Equation of Van der Pol-Duffing oscillator is considered in present work as mathematical model of cerebral circulation. The mathematical test of aneurysm presence in blood vessel for this mathematical model is obtained. The highest reliability of the test is 75% for internal carotid artery proofed clinically. The test obtained is provide to detect cerebral aneurysm without MRI or CT investigation by using perspective intravascular measurements. Supp. RFBR (14-01-00036)

Parathyroid hypertensive factor (PHF) - β2-adrenergic receptor potential antagonist

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The main effect of PHF consists in a long rise of blood pressure. This effect could be determined by the β2-adrenoceptor type involved in this process. In order to evaluate arterial hypertension formation it is worth noticing to study PHF molecular interactions with β2-adrenergic receptors. There are two important amino acids groups inside this receptor binding site - Asp113, Asn312, Tyr316 and Ser203, Ser204, Ser207 which could interact with the different ligand types. The antagonists (carazolol, timolol) form only one hydrogen bond with serine (Ser203 or Ser204). Docking program MolSoft ICM 3.8-3 Pro [http://molsoft.com/ Abagyan and Totrov, 1994] was used to calculate the position of agonists (epinephrine, clenbuterol) and antagonists (karazolol, pindolol) inside the β2-adrenergic receptor. We have docked PHF into the binding site of the β2-receptor with C-end (arginine) and N-end (tyrosine) also. The binding energy for N-end with Ser207 was found to be better by energy value.

Probabilistic theory of ions binding to RYR-channel within the improved electron-conformational model

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Ryanodine receptors (RyRs) form a class of intracellular calcium channels in various forms of excitable animal tissue like muscles. The studies of RyR's dynamics in vitro show it's stochastic character in case of stationary conditions. Here we introduce the improved Electron-Conformational model (ECM) of RyRs dynamics, which takes into account inactivated state of the RyR and a detailed description of Ca^{2+} binding to the RyR. The model considers two

generalized binding center channel: activation and inactivation surrounded by a sufficiently small area, where may fall Ca^{2+} ions. This neighborhood is considered to be discrete, the dimension is z "places". If at least k Ca^{2+} ions fall on a neighborhood of the binding sites the electronic transition occurs. The probability of electron transition can be described by the Binomial distribution. This method allowed describing the influence of Mg^{2+} (as an inhibitor) and ATP (as an activator) on RyR's opening-closure process. Supp. RSF 14-35-00005.

Stoichiometric modeling of oxygen transport through the surface of the isolated perfused rat liver at various oxygenation conditions

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Stoichiometric model of the metabolism of isolated perfused liver was developed to identify characteristics of oxygen transport through the surface of the isolated perfused liver. Flux Balance Analysis that is the optimization modeling method was used in simulation. The values of the O_2 consumption rate through the bloodstream and through the surface, the CO_2 release rate in the blood stream, the glucose consumption rate and release of lactate and urea obtained during perfusion of rat liver were used as the constraints in the model. Simulation showed that in order to maintain oxygen transport across the surface of the isolated perfused liver under normoxic conditions requires 2 ATP molecules but under reduced oxygenation of the perfusion medium – 7 ATP molecules. Thus, the oxygen transport through the surface of the isolated perfused liver affected by the lack of oxygen in the perfusion medium. This fact could be applied to the transplantation to assess the metabolic state of organ.

Theoretical modelling of magnetic hyperthermia

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Magnetic hyperthermia attracts considerable interest because of perspective of its usage for the tumor decease therapy. This method is based on the ability to produce heat acting by an alternating magnetic field on ferromagnetic nanoparticles placed in a carrier medium. If the particles are injected in a tumor, the tumor cell temperature would rise. The ill cells perish when their temperature achieves the range 42°C–46°C; this leads to the therapy effect. To the best of our knowledge, the theoretical investigations of the hyperthermia deal with the simplest approximation of the non-interacting particles. This simplification can be applied only to the systems with very low concentration of the particles. The obvious way to enforce the hyperthermia effect is to increase the particle concentration in the tumor region. However starting with some concentration of the particles, their interaction can not be ignored. In the present work we study effect of magnetic interaction between the single-domain nano-sized ferromagnetic particles on the hyperthermia effect produced under the action of the linearly polarized oscillating magnetic field.

Translational medicine. From basic science to clinical practice

Features of the regenerative processes in the rat liver exposed to alloxan diabetes with stimulation of macrophages functional activity

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The possibility of targeted correction of regenerative processes in the liver using 3-aminoftalgidrazid (AFG) stimulation of macrophages activity was studied on the model of alloxan diabetes in rats. It has been established that the introduction of AFG leads to normalization of blood biochemical parameters and reduces liver alteration. The morphometric analysis of hepatocyte reparative reactions confirmed the positive effect of AFG. The number of proliferating Ki-67-positive hepatocytes was significantly increased compared with the group without treatment but was lower than the values in intact rats. The inadequate proliferative activity of hepatocytes substituted by increase the intracellular regeneration and polyploidy indicating compensatory intensification of hepatocyte functional activity. These findings justify the use of the immunomodulators in treatment of liver diseases.
This work was supported RSF grant, project № 16-15-00039

The response of macrophage to chronic hyperglycemia before and after modulation of macrophage functional phenotype

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Hyperglycemia induces activation of ROS/RNS and inflammatory cytokine secretion by macrophage which is assumed as a major cause of the clinical complications of diabetes. The macrophage is able to change its functional phenotype from inflammatory to anti-inflammatory. The modification of macrophage reaction may improve adaptation of tissues and organs. We studied the distribution of macrophages (CD68) in animals with alloxan diabetes. We showed the increase in the amount of macrophages in pancreas and in primary lymphoid organs (marrow, thymus, spleen) in rat with alloxan diabetes. The modification of macrophage functional phenotype by tetrahydrophthalazine decreases in the amount of CD68+ cells in pancreas and thymus but does not change their content in spleen. Therefore, the modification of macrophage functional activity contributes to diminution of inflammatory by redistribution of CD68+ cells in pancreas and lymphoid organs. The investigation is supported Program of UB RAS №15-3-4-17

Specific features of the functional geometry of the left ventricle in myocardial diseases

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Functional geometry of the left ventricle (LV FG) of the heart refers to the dynamical change in the LV shape during contraction and relaxation. It has been shown that LV FG significantly contributes to the regulation of contractility and cardiac pump function in health and disease. The aim of our work is to evaluate the LV FG in patients with various myocardial diseases. The spatio-temporal heterogeneity of the LV regional wall motion is one of the characteristic features of normal cardiac pump function, which is shown to increase significantly in patients correlating with decreasing pump function. Some of the LV shape indexes essentially change in patients as compared to the control group depending on the decrease in the systolic function and LV geometry remodelling. In particular, ROC analysis identifies end-diastolic sphericity index and end-systolic Fourier power-shape index as having diagnostic significance to discriminate the group of patients from the control. Supported by RSF #14-35-00005 and Program RAS I.33П

Multiscale modeling of angiogenic tumor growth and progression

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It is well-known that under metabolic stress malignant cells produce chemical mediators which stimulate angiogenesis – the process of new vessels, basically capillaries, formation. So the question “how an increase in capillary network density influences the nutrient supply to a tumor” is significant for cancer research. This question is complex as these dependences are different for oxygen and glucose – two main nutrients for tumor growth. Accurate calculation of these nutrient fluxes to the 1 cm radius tumor requires computation of microcirculation through network consisting of more than one million capillaries each with diameter less than 10 microns. Obviously, this is a task for multiscale modeling. We introduce such model of tumor growth with account of angiogenesis and consider how oxygen and glucose fluxes alter in different stages of tumor progression. This is important for the design of new anticancer drugs, which are sensitive to metabolic changes in malignant cells.

Laser flash photolysis in investigation of breast cancer at different stages of tumor development

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The difference of hair microstructure and mammary cells of healthy and cancer carrier mice has shown for improving the optical techniques of non-invasive diagnostics of cancer diseases. The object of the research was wool and mammalian cells of mice (line BYRB) with spontaneous cancer tumors of mammary gland. Tumor size was from 0.5 to 3 cm. It was investigated by microscopy methods and laser-flash photolysis. Wool of healthy mouse has dense structure, external layer with large scales is pronounced. At the time, wool of mice with

cancer tumor is thinner, external and internal layers are destroyed. Length of scales is shorter. There is difference even when tumor diameter is 0.5 cm. Oxygen concentration increases during tumor development. It is related to reactive oxygen species rising within external layer of wool. Reactive oxygen species have most distribution in general oxygen concentration in external cell layer. Similar dependence was observed for cancer mammary cells.

Genetic and epigenetic aspects of neurodegenerative diseases etiopathogenesis

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The development of therapeutic strategies for treatment of socially important diseases, such as neurodegenerative diseases (NDD), is a main goal of experimental medicine. At most, NDD are sporadic polygenic syndromes with late onset, progressive memory loss, relentless progression and finally death. In a long run NDD have been sequentially envisioned to result from excitotoxicity, then from protein folding alterations, later on from chaperone defects and finally from actin cytoskeleton impairments. At present, while shifting from genetic to epigenetic aspects of NDD, all these considerations have merged. For instance, microRNA dysregulation is believed to be a main cause of NDD, a certain microRNA being a biomarker of a certain disease. To develop new generation therapeutics, new approaches and animal models are urgently required. Therefore, a research on Drosophila mutants with phenotypes similar to NDD diagnostic manifestations is very promising.

Electron microscopy in the diagnosis of male infertility

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A serious health problem is infertility, affecting about 15% of couples of reproductive age. Common causes of male infertility is a varicocele and cryptorchidism, diagnosed in childhood and adolescence. Revealed ultrastructural changes seminal walls of veins in varicocele may indicate malformation spermatic vein and its accompanying endothelial dysfunction, leading to ischemia and impaired testicular spermatogenesis. Cryptorchidism occurs when undescended testes into the scrotum before birth of a boy. Electron microscopic examination of testicular biopsies with cryptorchidism revealed pronounced destructive changes of the germinal epithelium of the seminiferous tubules, testicular sclerotic changes. Factors causing impaired fertility men are well studied and described in detail. Electron microscopy method reveals features of the ultrastructural organization of sperm exposed to damaging factors.

Influence of the pericellular microenvironment to the functional liver cells damaged by toxin

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The sinusoidal cells (SC) and mast cells of the liver regulate both destructive and regenerative processes in toxic hepatitis.Toxic hepatitis was simulated by the injection of carbon tetrachloride. Analysis of histological sections, immunohistochemistry and morphometric data showed that the manifestations of destructive-reactive inflammation phase in the liver of rats on the third day of the experiment were highest. Reduced signs of the exudative inflammation, to the 7-th day did not prevent progressive accumulation of mast cells and damaged hepatocytes. Reducing of the hepatocyte proliferation and the number of SC shows the exhaustion of compensatory SC features and justifies the use of immunomodulators affecting the SC. The study was conducted as a part of the budget program "Study of mechanisms of regenerative processes in organs and tissues using experimental models of extreme factors and toxic effects on the organism», state registration № 01201352042.

The dynamics of the regenerative processes in the retina in rats with alloxan diabetes and after injection of tetrahydrophthalazine derivatives

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Diabetes type 1 results in pathological changes in the retina, which leads to reduction of vision. Thereby, the search for new treatment of ocular disease in diabetes is an important problem of medicine. We investigated the possibility of correction of the retina damage in the alloxan diabetes using tetrahydrophthalazine derivatives (THP) having anti-inflammatory effects. The decrease in proliferative activity of cells in inner nuclear and ganglion layers of the retina was found in diabetic animals with staining by the proliferation marker Ki-67, which led to a reduction of retinal thickness. Injection of THP in diabetic animals contributed to recovery of proliferative activity in the inner nuclear layer of the retina and its activation in the ganglion layer which led to a partial recovery of retinal thickness. Thereby, the THP derivatives induce activation of the regenerative processes in the retina. The study was performed by a grant from the RSF (Project № 16-15-00039).

Mathematical modelling of the kidney transplant outcomes

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The study was aimed at determining the factors associated with the state of cadaveric donor kidney, affecting the results of transplantation.Recipients who take kidneys from older donors have longer term of creatinine normalization. Partial correlation between the donor diagnosis and the number of dialysis after surgery (the donor ageexcluded) indicate the cerebrovascular accident group has higher risk of head trauma group. The long time donor spent in the intensive care unit and high level of donors ALT predicts worse survival of patients and grafts. Use of vasopressors was signifficantly associated with DGF. The low donor serum sodium level predicts the worse survival of recipients and kidneys. The number of hemodialysis procedures after transplantation was correlated with the donor creatinine level. Insufficient daily dieresis of donor predicts worse grafts survival. High level of donors ALT predicts worse survival of patients and grafts.

Hemodynamics and regulation of angiogenesis in human embryo conceived by in vitro fertilization

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The concentrations of pro- and antiangiogenic growth factors, NO stable metabolites in maternal serum and embryonic left ventricular (LV) isovolumic relaxation time (IRT, ms) during the first trimester were assessed in two groups of women: with pregnancy conceived by in vitro fertilization (IVF, n=39) and normally conceived (control group, n=68) pregnancy. The concentration of vasoconstrictor endothelin 1 was 45.5 times more in IVF than in control group. On the contrary, the concentrations of NO stable metabolites in IVF was 1.9 times less than in control women. The assessment of angiogenic supressors in IVF women demonstrates the decrease in s-endoglin concentration in 1.6 times and in soluble receptor to vascular endothelial growth factor concentration in 2.0 times in comparison with control group. There was a significant increase in LV IRT in IVF embryos in comparison to control ones. These data suggest significant influence of preconceptional factors on embryonic angiogenesis and vascular impedance confirming the “intrauterine programming” theory.

Methodological approaches to identification of Systemic Inflammation under sepsis

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Development of the Systemic Inflammation (SI) under aseptic (trauma, bleeding etc.) diseases and different variants of septic process is well-known. Some critical clinical conditions such as multiple organ failure, disseminated intravascular clotting, and shock are exactly associated with SI. We describe systemic inflammation as a common pathophysiological process rather than syndromic model that is worldwide considered. SI is

registered by rates of systemic proinflammation cell stress products in plasma: cytokines and other inflammation mediators (more than 200) as well as by range of signs of different processes, which are associated with SI development. Thereto we have used ourselves developed scales to estimate both of Systemic Inflammatory Response and SI. A diagnostic efficiency of these scales is evaluated and systemic inflammation is described in patients with sepsis (n=207).

Medical chemistry

On correction and prevention of magnesium deficiency

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Objectives We aim to study the prevalence of magnesium deficiency among students and to analyze abilities of various hygiene factors for correction of magnesium deficiency. Research methods and resources The research was performed in a group of 70 people who are healthy USMU students aged 19-20. First, we estimated magnesium content in their blood plasma and saliva. Risk of magnesium deficiency development was studied in a questionnaire. Second, out of 70 probationers we chose a group of 30 students who showed low magnesium at the moment of research. The group kept to diet meals for two weeks. At two weeks intervals they took 50 mg DONAT magnesium rich water daily during 7 days. Research results On the basis of laboratory research, 50% of the students revealed magnesium deficiency, while the data of a previously taken questionnaire prevented us from finding out the risk of its development. As measures of correction and prevention of magnesium deficiency, DONAT water proved more effective compared to the food. Results of a physicochemical analysis of food have proved that their magnesium content doesn't correspond to previously known data and leads to low productivity in refilling magnesium deficiency.

Biological active trace elements of medicinal leeches Hirudo medicinalis L., 1758 and Hirudo verbana Carena, 1820, grown in artificial conditions of regional biofactories in Russia

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The Aim: The work is devoted to investigation of species and regional peculiarities of microelements composition in tissues of medicinal leeches, widely used in hirudotherapy and pharmacology. Methods: In studies used leeches adults of two species: Hirudo medicinalis L. 1758 and Hirudo verbana Carena, 1820. These leeches are grown on biofactories of different regions of Russia: “International center of medical leeches” (Moscow region), “HirudI.N.” (Saratov region), “Hirudo-Med.Yug” (Krasnodar region), “SibMedPiyavka” (Altai region). The concentrations of Cu, Zn, Mn, Fe, Ni, Cd, Pb in the tissues of the leech was determined by the method of atomic absorption spectrometers. Results: Estimation of elements contents in tissues of both species showed that they very much differed in concentration of essential elements - Cu, Fe and xenobiotic – Ni ($H2{,}45 > 28.8$; $p < 0.001$). Identified differences in elements spectrum in tissues of H. medicinalis and H. verbana can be used for directional selection in hirudotherapy and pharmacology.

1,3,4-thiadiazine derivates – antioxidants and protein glycation blockers – for correction of experimental diabetes mellitus

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In in vitro experiments demonstrated the ability of 1,3,4-thiadiazines differing substituents in the position 2- and 5- of heterocyclic ring, exhibit antioxidant activity and ability to block protein glycation. In in vitro screening results, selected a group of 1,3,4-thiadiazines, showed the ability to correct metabolic disorders (hyperglycemia, accumulation of protein glycation products and free-radical oxidation of lipids) in alloxan diabetes in rats. The mechanisms of action in vivo and interrelation "structure - activity" of the compounds discussed. This work was supported RSF grant, project number 16-15-00039.

Modelling of {Mo72Fe30} electrophoresis

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One of the potential candidates for the role of so-called “nanocontainers” for targeted drug delivery is a Fullerene-shaped nanocluster polyoxomolybdate (POM). To determine the capability of penetration of POM ions and their associates with biologically active substances through the skin patch, the experimental installation was developed. It consisted of two reservoirs divided by skin patch. To the both of reservoirs the electrodes were attached. On the first step, the diffusion coefficients (diffusivity) of POM and its associates in skin were estimated using the experimental data. On the second step, the numerical solutions of Nernst-Planck equation were obtained using the model of homogeneous, one-layered membrane and experimentally determined diffusion coefficients. We obtained the concentration profiles of permeant substance in membrane. These results allow us to estimate the velocity of electrophoretic delivery and accumulation of POM and it’s associates in skin layer.

Poly(ADP-ribose)polymerase 1 is one of the targets for the anti-cancer drugs search

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The DNA repair systems have a positive effect on the cells. They use these systems to ensure the genome stability. Anti-cancer therapy includes exposing the organism to agents that damage DNA. Thus, the DNA repair activity of cancer cells makes the system insensitive to therapy. The usage of DNA repair enzyme inhibitors can be a solution of this problem. Poly(ADP-ribose)polymerase 1 (PARP1) is one of the potential targets of the inhibition. This enzyme is critical for the regulation of the repair system activity. The aim of our work was to create a test system for in vitro studies of PARP1 activity. Our method can be used in real time and allows us to analyze two important steps: DNA-enzyme binding and dissociation of the DNA-enzyme complex after poly(ADP-ribosyl)ation. Our results suggest the possibility of using this test system for the screening studies to identify novel PARP1 inhibitors and analysis of enzyme-enzyme interactions.

Synthesis and antiviral activity of nitrile-containing 1,2,4-triazolo [5,1-c]-1,2,4-triazines

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A method for synthesis of antiviral drug “Triazavirine” analogue - 1,2,4-triazolo[5,1-c]-1,2,4-triazines containing nitrile group at 6-position - is developed. One of the synthesized compounds has exhibited a moderate antiviral activity in vitro against influenza virus A strain. In in vivo experiments on a model of lethal influenza infection in mice, the investigated compound has exhibited a high level of antiviral activity comparable with the action of oseltamivir and “Triazavirine”. While the acute toxicity study of drug on white mice it has been established that it belongs to practically non-toxic medicinal substances.

New perspective series of adenosine receptors inhibitors

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Well known that the daily use of just one cup of coffee reduces the likelihood of development of Parkinson's disease by five times. This effect is due to the action of caffeine on adenosine receptors. Thus, many recent studies have focused on the search for new antagonists of adenosine receptors. We have proposed a series of structural analogs of ZM-241385 - 6-nitro-7-aminotriazolo[1,5-a]pyrimidines and methods for their synthesis. In this case, the nitro group in the 6-position of the heterocyclic skeleton models electron-seeking nitrogen atom in the structure of the triazine compound ZM-241385 and our synthetic scheme offers wide possibilities for structural modeling molecular fragments for regulating the biological activity, while maintaining high receptor affinity. Our method involves obtaining the final products through respective chloroderivatives, the latter are synthesized from readily

available triazolopyrimidones.

The estimate of the concentrations of macroelements and trace elements in the biological system of obese pregnant women: (blood of mother – placenta – blood of newborn babies)

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According to World Health Organization over 1.5 billion people suffer obesity, 2.8 million die from obesity yearly. Pregnant obese women require an early diagnosis and prophylaxis of pathogenetic disturbances, as they cause obstetric complications (insufficiency of placenta, gestosis, intra-uterine hypoxia and intrauterine growth retardation of the fetus, and mortality among the newborn babies). Aim: A research on the contents of macroelements and trace elements in the biological system of obese pregnant women: (blood of mother – placenta – blood of newborn babies). Methods: standard laboratory analyses, functional assays, statistical methods. Results: The peculiarities of pregnancy and parturition in 96 women with alimentary obesity were investigated. The disbalance of essential and trace elements indicate their direct or indirect participation in the activation or inactivation of the main biochemical factors, involved in pathological processes, promoting alimentary obesity in pregnant women.

Associates of Mo72Fe30

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Presently we perform a complex investigation of a compound with literary designation: Mo72Fe30 as a base of targeted drug delivery system. Spherical structure with a cavity inside and the ability to complexation makes Mo72Fe30 a nanocontainer or a core-carrier for drug molecules. Unlike many of nanostructures Mo72Fe30 decomposes in the body over time into simple and harmless compounds that solves the problem of its removing. Preliminary studies did not reveal toxic effects on experimental animals (rats). The possibility of covering of Mo72Fe30 with biocompatible polymers: polyvinylpyrrolidone, polyethylene glycol was shown. We realized the creation of associates of Mo72Fe30 with insulin, vitamin B1, albumin. The particle size of associate of Mo72Fe30 with vitamin B1 was determined, it was about 56 nm. We plan to study the possibility of association of Mo72Fe30 with other drugs, as well as the study of the possibility of attachment to Mo72Fe30 the homing proteins in the future.

The study of the effects of L-arginine and taurine-contains drugs on platelet aggregation performance and lipid metabolism in patients with heart diseases

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The purpose of research was study of influence L-arginine and taurine-contains drugs on platelet aggregation and blood's lipids from patients with coronary heart disease. At this study were used blood samples from 72 volunteers of both sexes (age 54±5) with coronary heart disease, who treated with drugs contains L-arginine and taurine substances. Activity of platelet's aggregation in vitro was measurement by turbidimetric method with using laser four-platelet aggregation analyzer with using standard aggregation inducers. The lipid's profiles were measurement by an enzymatic method with using automatic biochemistry analyzer. The results of this study show that the combination of drugs which contains L-arginine and taurine substance were leaded to reduction at platelet aggregation activity. Admission of the L-arginine and taurine in the basic therapy were accompanied by a significant change in the blood's lipid spectrum and leaded to decrease on total cholesterol and its fractions.

Nitroacetonitrile is the intermediate for the synthesis of azolo-6-azapurines

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The thesis provides information about the synthesis of azolo-6-azapurines as potential biological activity due to structural analogy with natural purines.

Biomedical technology

The study of cardiomyocyte structure by scanning probe nanotomography

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Interaction between cardiomyocytes and nanofiber scaffolds is studied in this work. Understanding of the mechanism of interaction between the heart cells and their physical environment is necessary for determination of development and proliferation of cardiomyocytes, as well as for the selection of the substrate topology and configuration, suitable for the creation of tissue-engineering constructs, which can be applied for regeneration of a damaged heart tissue. To study this interaction, the method of scanning probe nanotomography ("slice and view" technology, ultramicrotome combined with atomic-force microscope) is used. It allows to acquire data on the spatial structure of an object with nanometer resolution. The presence of the coherent some interface between cardiomyocytes and nanofiber scaffold at different configurations of the latter is showed. Besides, the possibility of studying cardiomyocyte ultrastructure with the help of atomic-force microscopy is demonstrated.

Development of the way of early diagnostic of essential arterial hypertension different forms in adolescents

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Early stages of essential arterial hypertension (EAH) in adolescents are complex to diagnose. A new diagnostic test, which allows establishing the diagnosis, was created. It is based on a concept of that early changes in EAH are a disturbance of endothelial function which forms endothelial dysfunction which consists in three key vasoactive factors imbalance – nitric oxide (NO), endothelin-1 (ET-1), serotonin (5-HT). 2 stages of research were performed: EAH models, immature SHR rats (1) and patients with different forms of EAH (2). NO (colorimetry) and 5-HT content in serum, ET-1 in plasma and 5-HT in platelets (ELISA) were measured. Results: 1. NO content was 14,7% higher, ET-1 was 2,9 times higher, 5-HT in blood plasma and platelets was 2,7 and 2,3 times higher in SHR, respectively. 2. NO content was 52%, 88% lower of 100% of healthy adolescents in stabile and labile forms, respectively, ET-1 was 738% and 1833% higher, 5-HT - 292% and 315% in serum, 200% and 300% in platelets higher.

Training for biomedical engineering at the Ural Federal University

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The Physics and Technology Institute (PhysTech) started training programs in the field of biomedical engineering in 2000. The main purpose of the educational program was the training for the development and service of high-tech medical equipment. Basic physical and technical training in mathematics, theoretical and applied physics were supplemented by the special sections of biophysics, electronics, construction of biotechnical and medical systems. Student's research constitutes one of the most important components of the education program. The PhysTech provides wide opportunities for multidisciplinary projects (for example, preparation of cerium oxide nanoparticles with the aim of developing new contrast materials for MRI or effecting on cell cultures to suppress various pathologies). To expand the opportunities of biomedical engineering education we develop molecular imaging methods. To produce the isotopes for this purpose we create a cyclotron nuclear medicine center.

CD45RA+ T-lymphocytes levels evaluation in thymus of rats of various age groups in relation to dietary regimen

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Naïve T-lymphocytes are cells which have not experienced any antigen contact. Their main function is to react to new pathogens. During the aging process these cells concentration drops and this influences the body resistance to various infections. This experiment involved 34 rats of 3 age groups: 6, 12 and 18 months old. The animals of control group were feed ad libitum. The amount of food for the test group was reduced by 50% during 2 months. CD45RA+ concentration in thymus is significantly reduced with age. In the group of 6 months old rats the amount of naïve t-lymphocytes was 7.1%, and 5.3% in 12 months old rats. It's hard to define areas of concentration of these cells in 12 and 18 months old rats and the membranes are coloured unevenly. Thymus of rats taking less food had CD45RA+ level dropping faster, compared to control group animals. It is possible, that acute food deficiency is a negative factor for the animal, and reduces adaptive capacity of the immune system

Influence of radiation therapy on implantable cardiac pacemakers

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The rapid development of technologies for radiotherapy promotes quality irradiation of cancer patients. The number of patients with implantable pacemakers is increasing. Irradiation of such patients can cause malfunction of electronic devices. It is well known that secondary neutrons are the main cause of failures, therefore proton and photon radiotherapy (with energies above 10MeV) is contraindicated in patients with pacemakers. In Masaryk Memory Cancer Institute 6 implantable cardioverter defibrillators and 18 pacemakers from different manufacturers were tested on LINAC-2100CD accelerator by VARIAN firm in the treatment mode 40x2Gy=80Gy. Malfunctions were observed in 5 devices. Some of them were capable of functioning after reprogramming, but several failures were fatal to the future usage. The data obtained from this experiment are important for planning physicists when

selecting the radiation techniques and suitable method of planning of the irradiation of patients with pacemakers.

RBC morphology according atomic force microscopy and metabolic disorders in alloxan diabetes in rats

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The morphology of the red blood cells (RBC) has been studied by atomic force microscopy (AFM) in contact with indicators of disturbed metabolism in experimental diabetes mellitus (DM) in rats. DM was modeled by administration of alloxan in a dose of 300 mg / kg body weight. After 1 month of DM modeling according to AFM data the RBC have an uneven surface, spinous outgrowths membrane. The proportion of such cells (echinocytes) was at DM 78.9% in the control group - 17.6%. RBCs of rats with DM also have a smaller diameter, a greater height and lower values of adhesion, compared to the control. The study of biochemical parameters revealed a pronounced hyperglycemia, and high levels of HbA1c, but the status indicators of oxidative stress (MDA, catalase, peroxidase), not significantly different in the two groups of animals. Thus, the AFM shows the violation morphology of RBC in experimental DM, leading role in the development of which plays hyperglycemia and glycation of proteins.

The interaction between the cell culture and bimodal nanoparticles with structure: fluorescent core - silica - magnetic nanoparticles

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The relevant task of nanotechnology is development of bimodal nanoparticles with magnetic and fluorescent characteristics simultaneously to combine and improve existing methods of analysis. The magnetic component of bimodal nanoparticles permits to use magnetometrical methods (Faraday balance and SQUID) and methods of relaxometry (NMR and MRI). Fluorescence allows to apply confocal microscopy and flow cytometry. The research investigates an interaction between bimodal nanoparticles with orbit-like structure and cells. The localization of magnetic nanoparticles which surround a fluorescent core leads to increase in relaxivity that is important for NMR and MRI. The fluorescent component of nanoparticle is low-toxic carbon quantum dots encapsulated in the matrix of silicon dioxide; the magnetic compound is iron-carbon nanoparticles. The investigation carried out on cell culture HeLa and rat fibroblasts using confocal microscopy, flow cytometry, relaxometry and magnetometrical methods.

Ceria nanoparticle cytotoxicity research

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Nanoparticles (NP) are supposed to be used in many fields, including medicine, due to their unique properties. However, the NP properties primarily depend on preparation methods and conditions. Ceria NP can generate diverse quantities of ROS subject to the environmental acidity. The fact of the matter is that healthy and cancerous cells provide pH different atmosphere. The level of ROS generated by ceria NP appears to be enhanced in the slightly acidic cancerous cell environment that causes cell death facilitation. Ceria NP obtained by electron beam evaporation were applied to rhabdomyosarcoma, HEK-293, HeLa cell lines and human fibroblasts. There was a slight reduction in the viability of all cell cultures at low NP concentrations (up to 100 μg/ml). The sharply cancerous cell viability reduction is observed with concentration increase while the normal cell viability remains unchanged. The lethal concentration which means the half cancerous cell death is found to be at 500 μg/ml level.

Effects of weak static magnetic field on cognition

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Actual problems of modern neurophysiology is the study of the prerequisites of socially significant diseases, which arise spontaneously and unpredictably as a result of large deletions and duplications in the unequal recombination in regions of chromosomes with a specific architecture, often their appearance may affect the external factors, such as stress, temperature effects, radiation. The high frequency of these structural rearrangements of the genome, much higher than the frequency of the disease due to mutations in a single gene, attracted the attention of physicians and led to the formation of the concept of "genomic diseases". In our report, we examine the effect of ambulance station on line learning and memory processes Canton-S and Drosophila GNS3 and it has been shown that the observed under the influence of Ambulance Station suppress transcriptional activity may be due to multiple violations of various cell signaling cascades.

The method of dynamic correction of the neck nerve structures conduction activity and its place in modern medicine

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The report focuses on non-invasive multi-channel neuromodulation technology, and one of the methods of its implementation - dynamic correction of the neck nerve structures conduction activity. The history of the method, experimental and clinical studies, applications in medical practice and hypothesis of neuromodulation mechanisms are discussed.

The use of coherent superheterodyne ESR spectrometer for measuring radiation dose

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The purpose of work is quantitation of the dose of ionizing radiation using electron spin resonance phenomena (ESR). To date, photographic and other methods are widely used on practice. The negative sides of these methods are large inaccuracies during measurements. Method for determination of absorbed dose by ESR provides higher performance in terms of accuracy of dose determination. In this work we are using latest ESR spectrometer, developed by UrFU and NPOA. It wins against its rivals in size, versatility and precision. The alanine strips are used as the detector strips. Alanine free radical gives typical ESR signal, which intensity is proportional to absorbed dose, but depends on the power and energy of radiation. Our strips are irradiated with different doses. The spectrums are displaying as calibration curve dependent on the dose of the central peak amplitude. Calculation of the absorbed dose can be based on this curve and this method can be used as collateral during tomotherapy.

Morphological assessment of efficiency of pharmaceutical composition based on silicon organic glicerohydrogel

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The aim of the study was to analyze the histological results in the model of chronic periodontitis in rats using medicinal compositions: №1 -Polioksidony with silicon organic glicerohydrogel and №2 - Betaleukin with silicon organic glicerohydrogel, compared with the group without medical treatment. From the histological characteristics in the group with Betaleukin, by the end of the study obtained data showed preserved resorption of alveolar bone, with increasing of the capillary vessels in the area of chronic inflammation. Immunomodulatory characteristics of Polyoxidonium applied in the second group of experimental animals had a positive impact on the process of repair of periodontal tissues, including bone, in rats. In the group of animals without treatment the processes of regeneration of the alveolar bone and connective tissue structures were observed, restoring submucosal occurred by the type of scarring.

Drosophila as a tool for unravelling microRNA biomarkers of neurodegenerative diseases

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Current notion that neurodegenerative disorders (NDD), such as Alzheimer's (AD); Parkinson's (PD); Huntington's (HD) diseases may result not from a mutation of a single gene, but rather from dysregulation of miRNAs (miRs) bases on the fact that one miR can alter the expression of hundreds of genes. The identification of miRs biomarkers of NDD has recently started. Studies in Drosophila have pinpointed that the miR PD biomarker is let-7/miR-184*. The target gene of let-7 is LRRK2 involved in regulation of the cytoskeleton and interacting with the partner genes of LIMK1, the key enzyme of actin remodeling, namely, Parkin. AD biomarker is miR-34, its target genes are tau, creb, hsp70. HD biomarker is miR-9. The content of these miRs is altered in the Drosophila mutant agnts3 isolated in our lab. agnts3 carries a ts-mutation in dlimk1 gene and can serve as a model for PD Dementia with Leavy Bodies. Our findings in mutant and wild type Drosophila strains unravel the miRs role in cognition.

The changes in morphofunctional state of cultured cells under the influence of polyoxometalates

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We studied the influence of molybdenum and iron-molybdenum nanocluster polyoxometalates on the morphofunctional characteristics of primary and continuous cell cultures for possible biomedical applications. The experiments were performed with different concentrations of nanoclusters (Mo72Fe30 and Mo132), which were added to the medium of cell culture. The study showed the lack of cytotoxicity of the cluster Mo72Fe30 for normal rat fibroblasts, decrease in proliferative activity and acceleration of differentiation of transformed rat fibroblasts on the day after influence. We revealed changes in the morphology of normal and transformed cells under the action of moderate concentrations of Mo72Fe30. The cytotoxic effects of nanocluster Mo132 were shown in regard to the transformed and normal cells. The study is financially supported by the resolution No. 211 of the Government of the Russian Federation contract № 02.AO3. 0006.

Van der Pol - Duffing oscillator as the rheology equation of the brain vasculature

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We consider the model of hemodynamic, built on the basis of clinical blood monitoring data, obtained during neurosurgical operations. The model links the blood flow velocity and pressure changes in the arterial cerebral vascular network. The model is the equation of a nonlinear oscillator (a generalization of the Van der Pol oscillator), velocity plays the role of right-hand side. The coefficients determined by the methods of the theory of inverse problems are individual for each patient. The model has proven its effectiveness on the data obtained in a variety of neurosurgical operations. Analyzes the resonance characteristics of the equation and their relation to hemodynamic.

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